ClinicalEvidence

Diarrhoea in adults (acute)

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ABSTRACT

INTRODUCTION: An estimated 4.6 billion cases of diarrhoea occurred worldwide in 2004, resulting in 2.2 million deaths. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of treatments for acute diarrhoea in adults living in resource-rich countries? What are the effects of treatments for acute mild-to-moderate diarrhoea in adults from resource-rich countries travelling to resource-poor countries? What are the effects of treatments for acute mild-to-moderate diarrhoea in adults living in resource-poor countries? What are the effects of treatments for acute severe diarrhoea in adults living in resource-poor countries? We searched: Medline, Embase, The Cochrane Library, and other important databases up to January 2010 (Clinical Evidence reviews are updated periodically, please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found 72 systematic reviews, RCTs, or observational studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review we present information relating to the effectiveness and safety of the following interventions: antibiotics, antimotility agents, antisecretory agents, bismuth subsalicylate, diet, intravenous rehydration, nasogastric tube rehydration, oral rehydration solutions (amino acid oral rehydration solution, bicarbonate oral rehydration solution, reduced osmolarity oral rehydration solution, rice-based oral rehydration solution, standard oral rehydration solution), vitamin A supplementation, and zinc supplementation.

QUESTIONS

INTERVENTIONS

DIARRHOEA IN RESOURCE-RICH COUNTRIES

TRAVELLERS' DIARRHOEA

MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES

SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Unknown effectiveness

Covered elsewhere in Clinical Evidence

Gastroenteritis in children

To be covered in future updates

Adsorbent agents

Footnote

*Categorisation based on consensus. RCTs are unlikely to be conducted.

Key points

- Diarrhoea is an alteration in normal bowel movement, characterised by increased frequency, volume, and water content of stools, often defined clinically as an increase in stool frequency to three or more liquid or semi-formed motions in 24 hours.

  An estimated 4.6 billion cases of diarrhoeal illness occurred worldwide in 2004, causing 2.2 million deaths, 1.5 million of which were in children.

- This review examines the effects of treatments in adults.

- In people from resource-poor countries, antisecretory agents, such as racecadotril, seem to be as effective at improving symptoms of diarrhoea as antimotility agents, such as loperamide, but with fewer adverse effects.

  Empirical treatment with antibiotics also seems to reduce the duration of diarrhoea and improve symptoms in this population, although it can produce adverse effects such as rash, myalgia, and nausea.

  Instructing people to refrain from taking any solid food for 24 hours does not seem to be a useful treatment, although the evidence for this is sparse.

  We don't know how effective oral rehydration solutions or antibiotics plus antimotility agents are in this population, as we did not find any RCTs.

- Antisecretory agents, antibiotics, and antimotility agents also seem to be effective in treating people from resource-rich countries who are travelling to resource-poor countries.

  Antibiotics plus antimotility agents may be more effective than antibiotics alone at reducing the duration of diarrhoea in people with travellers' diarrhoea.

  Bismuth subsalicylate is effective in treating travellers' diarrhoea, but less so than loperamide, and with more adverse effects (primarily black tongue and black stools).

  We don't know the effectiveness of oral rehydration solutions or restricting diet in reducing symptoms of diarrhoea in people travelling to resource-poor countries.

- For people from resource-poor countries with mild or moderate diarrhoea, antisecretory agents seem to be as beneficial as antimotility agents, and cause fewer adverse effects (particularly rebound constipation).

  We didn't find sufficient evidence to allow us to judge the efficacy of antibiotics, antibiotics plus antimotility agents, or oral rehydration solutions in this population.

- Oral rehydration solutions are considered to be beneficial in people from resource-poor countries who have severe diarrhoea.

  Studies have shown that amino acid-based and rice-based oral rehydration solutions are beneficial, but the evidence is less clear about the efficacy of bicarbonate or reduced osmolarity solutions.

  Rice-based oral rehydration solutions seem more beneficial compared with glucose-based oral rehydration solutions in reducing the duration of severe diarrhoea in resource-poor countries.

- We don't know whether intravenous rehydration is more beneficial than oral rehydration or enteral rehydration through a nasogastric tube.

  We don't know whether antimotility agents, antisecretory agents, antibiotics, or antibiotics plus antimotility agents are effective for treating people with severe diarrhoea in resource-poor countries.

  We found no evidence on the use of zinc or vitamin A supplementation in adults in a resource-poor setting.

DEFINITION

Diarrhoea is an alteration in normal bowel movement, characterised by increased frequency, volume, and water content of stools. It is often clinically defined as an increase in stool frequency to three or more liquid or semi-formed motions in 24 hours. Acute diarrhoea is usually defined as diarrhoea of 14 days' duration or less, while persistent diarrhoea is of over 14 days' duration. Diarrhoea of over 30 days' duration is frequently defined as "chronic". [1] This review examines the effects of treatments for diarrhoea in adults.

INCIDENCE/ PREVALENCE

The World Health Organization (WHO) estimated an overall incidence of 4.6 billion cases of diarrhoeal illness worldwide for 2004. [2] This incidence was associated with 2.2 million deaths. [2] Deaths due to diarrhoeal illness occur predominantly in children, with an estimated 1.5 million deaths in under 5-year-olds each year, making diarrhoeal illness the second leading cause of death in this age group. [3] In the USA, the estimated incidence for infectious intestinal disease is 0.44 episodes per person per year (1 episode per person every 2.3 years), resulting in about one consultation with a doctor per person every 28 years. [4] A community study in the UK reported an incidence of 19 cases per 100 person-years, of which 3.3 cases per 100 person-years resulted in consultation with a general practitioner. [5] Both estimates derive from population-based studies, including both adults and children. The epidemiology of travellers' diarrhoea is not well understood. Incidence is higher in travellers visiting resource-poor countries, but it varies widely by location and season of travel. [6] The incidence of diarrhoea in adults in resource-poor countries is largely unknown owing to the lack of large-scale surveillance studies in these countries.

AETIOLOGY/ RISK FACTORS

The cause of diarrhoea depends on geographical location, standards of food hygiene, sanitation, water supply, and season. Commonly identified causes of sporadic diarrhoea in adults in resource-poor countries include *Campylobacter*, *Salmonella*, *Shigella*, *Escherichia coli*, *Yersinia*, protozoa, and viruses (see table 1, p 30). [7] [8] No pathogens are identified in more than half of people with diarrhoea. In returning travellers, about 50% of episodes are caused by bacteria such as enterotoxigenic *E coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Vibrio*, enteroadherent *E coli*, *Yersinia*, and *Aeromonas* (see table 1, p 30). [7]

PROGNOSIS

In resource-rich countries, death from infectious diarrhoea is rare, although serious complications, including severe dehydration and renal failure, can occur and may necessitate admission to hospital. Elderly people and those in long-term care have an increased risk of death. [9] In resource-poor countries, diarrhoea is reported to cause more deaths in children under 5 years of age than any other condition. [10] Few studies have examined which factors predict poor outcome in adults.

AIMS OF INTERVENTION

To reduce the infectious period, length of illness, risk of dehydration, risk of transmission to others, and rates of severe illness; and to prevent complications and death, with minimum adverse effects.

OUTCOMES

Mortality; cure; illness duration (time from start of treatment to last loose stool; time to first formed stool; duration of diarrhoea; duration of fever, duration of excretion of organisms); symptom control (number of loose stools a day; stool volume; relief of cramps, nausea, and vomiting; incidence of vomiting; incidence of severe illness; need for unscheduled fluids); microbiological efficacy (eradication of pathogens); presence of bacterial resistance; rate of hospital admission; adverse effects.

METHODS

Clinical Evidence search and appraisal January 2010. The following databases were used to identify studies for this systematic review: Medline 1966 to January 2010, Embase 1980 to January 2010, and The Cochrane Database of Systematic Reviews 2009, Issue 4 (1966 to date of issue). An additional search within The Cochrane Library was carried out for the Database of Abstracts of Reviews of Effects (DARE) and Health Technology Assessment (HTA). We also searched for retractions of studies included in the review. Abstracts of the studies retrieved from the initial search were assessed by an information specialist. Selected studies were then sent to the contributor for additional assessment, using predetermined criteria to identify relevant studies. Study design criteria for inclusion in this review were: published systematic reviews of RCTs and RCTs in any language, at least single blinded, and containing more than 20 individuals of whom more than 80% were followed up. There was no minimum length of follow-up required to include studies. We excluded all studies described as "open", "open label", or not blinded unless blinding was impossible. We did not exclude studies that included people with HIV/AIDS. We included systematic reviews of RCTs and RCTs where harms of an included intervention were studied applying the same study design criteria for inclusion as we did for benefits. In addition we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 37). The categorisation of the quality of the evidence (into high, moderate, low, or very low) reflects

the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the *Clinical Evidence* population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION **What are the effects of treatments for acute diarrhoea in adults living in resource-rich countries?**

OPTION **ANTIMOTILITY AGENTS IN RESOURCE-RICH COUNTRIES**

Duration of illness

Diphenoxylate compared with placebo Diphenoxylate may be no more effective at increasing median time to last stool in adults with acute diarrhoea of <24 hours (low-quality evidence).

Loperamide hydrochloride/oxide compared with placebo Loperamide hydrochloride and loperamide oxide are more effective at reducing the duration of diarrhoea in adults (high-quality evidence).

Loperamide hydrochloride compared with loperamide oxide Loperamide hydrochloride and loperamide oxide seem to be equally effective at reducing the duration of diarrhoea in adults (high-quality evidence).

Symptom control

Diphenoxylate compared with placebo Diphenoxylate may be more effective at reducing the rate of bowel actions 24 hours after treatment in adults with acute diarrhoea (low-quality evidence).

Adverse effects

Loperamide hydrochloride and loperamide oxide have been associated with increased constipation-like periods.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found 6 RCTs. [11] [12] [13] [14] [15] [16]

Difenoxin:

We found no RCTs.

Diphenoxylate:

We found one RCT (152 adults with acute diarrhoea for <24 hours) comparing diphenoxylate–atropine versus placebo. It found that diphenoxylate significantly reduced the rate of bowel actions in the 24 hours after treatment (P = 0.05). [11] The RCT found no significant difference in median time to last loose stool (25 hours with diphenoxylate *v* 30 hours with placebo; P = 0.29).

Lidamidine:

We found no RCTs.

Loperamide hydrochloride:

We found two RCTs (409 [13] and 261 [14] adults with acute diarrhoea, defined as >2 watery or loose stools in the previous 24 hours) with 4 study arms each, comparing loperamide hydrochloride versus placebo and versus two doses of loperamide oxide (1 mg and 2 mg). Both RCTs found that loperamide hydrochloride significantly reduced duration of diarrhoea compared with placebo (first RCT: [13] median time to complete relief of diarrhoea: 27 hours with loperamide hydrochloride *v* 45 hours and 15 minutes with placebo; P = 0.006; second RCT: [14] median time to complete relief of diarrhoea: 17.5 hours with loperamide hydrochloride *v* 37 hours with placebo; P = 0.007). They found no significant difference among the groups on active treatment (first RCT, median time to complete relief of diarrhoea: 27 hours with loperamide hydrochloride *v* 23.5 hours with loperamide oxide 1 mg *v* 25.5 hours with loperamide oxide 2 mg; P >0.7; second RCT, median time to complete relief of diarrhoea: 17.5 hours with loperamide hydrochloride *v* 18 hours with loperamide oxide 1 mg *v* 18.5 hours with loperamide oxide 2 mg; P >0.8).

Loperamide oxide:

We found 5 RCTs comparing loperamide oxide versus placebo, versus loperamide hydrochloride, or comparing different doses of loperamide oxide. [12] [13] [14] [15] [16] The first RCT (230 adults with >2 watery or loose stools in the previous 24 hours) had three study arms and compared two doses of loperamide oxide (1 mg and 2 mg) versus placebo. [12] It found that both doses of loperamide oxide significantly reduced duration of diarrhoea compared with placebo (median time to complete relief of diarrhoea: 27 hours and 55 minutes with loperamide oxide 1 mg *v* 40 hours and

35 minutes with placebo; P = 0.022; 25 hours with loperamide oxide 2 mg *v* 40 hours and 35 minutes with placebo; P = 0.011).

The second and third RCTs had 4 study arms each and compared two doses of loperamide oxide (1 mg and 2 mg) with placebo and loperamide hydrochloride. [13] [14] Both RCTs found that both doses of loperamide oxide significantly reduced duration of diarrhoea compared with placebo (first RCT, median time to complete relief of diarrhoea: 23.5 hours with loperamide oxide 1 mg *v* 45 hours and 15 minutes with placebo; P = 0.009; 25.5 hours with loperamide oxide 2 mg *v* 45 hours and 15 minutes with placebo; P = 0.007; second RCT, median time to complete relief of diarrhoea: 18 hours with loperamide oxide 1 mg *v* 37 hours with placebo; P = 0.003; 18 hours and 30 minutes with loperamide oxide 2 mg *v* 37 hours with placebo; P = 0.012) and found no significant difference between the groups on active treatment (see loperamide hydrochloride above).

The fourth RCT (242 adults with acute diarrhoea, defined as >3 loose or watery stools in the previous 24 hours) compared two doses of loperamide oxide (0.5 mg and 1 mg) versus placebo. [15] It found that both doses of loperamide oxide significantly reduced duration of diarrhoea compared with placebo (median time to complete relief of diarrhoea: 25 hours and 40 minutes with loperamide oxide 0.5 mg *v* 34 hours and 15 minutes with placebo; P = 0.041; 26 hours and 30 minutes with loperamide oxide 1 mg *v* 34 hours and 15 minutes with placebo; P = 0.044). Investigators' ratings of overall efficacy of loperamide oxide 1 mg, using a 5-point scale, were significantly better than placebo (P = 0.008) but the difference did not reach significance between loperamide oxide 0.5 mg and placebo (P = 0.096). Similarly, participants' overall evaluations of the efficacy of treatment, using a 100-point visual analogue scale, were significantly better with loperamide oxide 1 mg compared with placebo (P = 0.003) but the difference did not reach significance between loperamide oxide 0.5 mg and placebo (P value reported as not significant; CI not reported).

The fifth RCT (258 adults with acute diarrhoea, defined as 4 or more watery or loose stools within the previous 24 hours, and with diarrhoea for no more than 72 hours) compared 4 interventions: loperamide oxide 1 mg, 2 mg, or 4 mg, or placebo. All participants were given an initial dose of two tablets and told to take another tablet on experiencing symptoms. All doses of loperamide decreased median time to relief of diarrhoea compared with placebo, but there was no significant difference between the three loperamide groups (median time to first relief: 28 hours and 40 minutes with placebo *v* 10 hours with loperamide 1 mg *v* 12 hours and 45 minutes with loperamide 2 mg *v* 7.5 hours with loperamide 4 mg). [16]

Harms:

Difenoxin:
We found no RCTs.

Diphenoxylate:
The RCT comparing diphenoxylate–atropine versus placebo gave no details on adverse events and possible attribution/relationship to treatment. [11]

Lidamidine:
We found no RCTs.

Loperamide hydrochloride:
The first RCT found that loperamide hydrochloride significantly increased the proportion of people with constipation-like periods compared with placebo (25% with loperamide hydrochloride *v* 7% with placebo; P less-than or equal to 0.002). [13] The second RCT (261 adults) compared loperamide oxide 1 mg with loperamide oxide 2 mg, with loperamide 2 mg, and with placebo. [14] Adverse effects were mainly gastrointestinal (4 people with loperamide oxide 1 mg *v* 4 people with loperamide oxide 2 mg *v* 6 people with loperamide 2 mg *v* 8 people with placebo; gastrointestinal adverse effects not further specified). The significance of the difference between groups in adverse effects was not reported.

Loperamide oxide:
The first RCT found that few adverse effects were reported and all were mild or moderate (3/70 [4%] people with loperamide oxide 1 mg *v* 1/72 [1%] people with loperamide oxide 2 mg *v* 3/71 [4%] people with placebo). [12] The second RCT found that loperamide oxide 2 mg significantly increased the proportion of people with constipation-like periods compared with placebo (24% with loperamide oxide 2 mg *v* 7% with placebo; P less-than or equal to 0.002), but found no significant difference between loperamide oxide 1 mg and placebo (16% with loperamide oxide 1 mg *v* 7% with placebo; reported as not significant). [13] The third RCT (261 adults) compared loperamide oxide 1 mg with loperamide oxide 2 mg, with loperamide 2 mg, and with placebo. [14] Adverse effects were mainly gastrointestinal (4 people with loperamide oxide 1 mg *v* 4 people with loperamide oxide 2 mg *v* 6 people with loperamide 2 mg *v* 8 people with placebo; gastrointestinal adverse effects not specified). The significance of the difference among groups in adverse effects was not reported.

The fourth RCT (242 adults) found that more people on placebo than loperamide oxide reported adverse effects but significance was not reported (7/83 [8%] people with loperamide oxide 1 mg *v* 3/79 [4%] people with loperamide oxide 0.5 mg *v* 16/80 [20%] people with placebo). [15] Abdominal cramps were the most frequently reported adverse effect in people taking placebo. In one person taking placebo, the cramps were noted as severe. The fifth RCT found that adverse effects of any kind reported after non-leading questions were 13/66 (20%) for placebo, 7/64 (11%) for loperamide oxide 1 mg, 13/63 (21%) for loperamide oxide 2 mg, and 14/65 (22%) for loperamide oxide 4 mg (significance of difference between groups not reported). [16] The proportions of people having a constipation-like period for 48 hours or more were as follows: 11% with placebo, 10% with loperamide oxide 1 mg, 25% with loperamide oxide 2 mg, and 25% with loperamide oxide 4 mg. There was no significant difference between loperamide oxide and placebo.

Comment:

Clinical guide:
There is evidence of benefit for antimotility agents, strongest for loperamide. However, antimotility agents are not recommended for people with suspected shigellosis or Shiga-toxin-producing *E coli.* [1]

OPTION ANTISECRETORY AGENTS IN RESOURCE-RICH COUNTRIES

Duration of illness
Racecadotril compared with placebo Racecadotril is more effective at reducing the duration of diarrhoea in people with acute diarrhoea (moderate-quality evidence).

Racecadotril compared with loperamide Racecadotril and loperamide seem to be equally effective at reducing the duration of diarrhoea in people with acute diarrhoea (moderate-quality evidence).

Symptom control
Racecadotril compared with placebo Racecadotril is more effective at reducing stool weight passed in the first 24 hours after treatment in people with acute diarrhoea (moderate-quality evidence).

Racecadotril compared with loperamide We don't know whether racecadotril is more effective than loperamide at reducing the number of diarrhoeal stools passed until recovery in people with acute diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

We found no systematic review, but found 5 RCTs comparing racecadotril (previously called acetorphan) with placebo or loperamide. [17] [18] [19] [20] [21]

Racecadotril versus placebo:
We found two RCTs comparing racecadotril with placebo. The first RCT (198 people with acute diarrhoea in France) found that racecadotril (200 mg loading dose, followed by 100 mg after each loose motion) significantly reduced mean duration of diarrhoea compared with placebo at 10 to 14 days (mean: 3.4 days with racecadotril *v* 4.4 days with placebo; P = 0.001). [17] However, 30 people were not included in the analysis as they still had unformed stools 24 hours before follow-up (7 [7%] people with racecadotril *v* 23 [24%] people with placebo). [17] The second RCT (71 people with acute diarrhoea in Tunisia) found that racecadotril (100 mg 3 times daily before meals) significantly reduced stool weight passed in the first 24 hours of treatment compared with placebo (mean: 355 g with racecadotril *v* 499 g with placebo; P = 0.025) and passed fewer stools (mean: 4.3 with racecadotril *v* 5.4 with placebo; P = 0.027). [18]

Racecadotril versus loperamide:
We found three RCTs comparing racecadotril versus loperamide. [19] [20] [21] The first RCT (69 people with acute diarrhoea) compared racecadotril (200 mg loading dose repeated at 12 hours, then 300 mg/day until well) versus loperamide (2 times 1.33 mg loading dose repeated at 12 hours, then 3 times 1.33 mg until well). [19] The RCT found no significant difference between racecadotril compared with loperamide in duration of diarrhoea (2.2 days with racecadotril *v* 2.3 days with loperamide; reported as not significant). [19] The second RCT (62 people with acute diarrhoea) found no significant difference between racecadotril (100 mg 3 times daily) and loperamide (2.0 mg twice daily) in mean duration of diarrhoea (19.5 hours with racecadotril *v* 13 hours with loperamide; P = 0.23). [20] The third RCT (157 people with acute diarrhoea) found no difference between racecadotril (100 mg loading dose and 100 mg 3 times daily before meals) compared with loperamide (4 mg loading dose and 2 mg after each loose stool) in the number of diarrhoeal stools passed until recovery (mean: 3.5 with racecadotril *v* 2.9 with loperamide; P value not reported). The total duration of diarrhoea after initiation of treatment was similar for both groups (mean: 14.9 hours with racecadotril *v* 13.7 hours with loperamide; P value not reported).

Harms:

Racecadotril versus placebo:
The frequency and nature of reported adverse effects were similar in the two treatment groups in one RCT (35% with racecadotril *v* 36% with placebo). [17] The adverse effects included nausea, thirstiness, vertigo, constipation, and headache. In the second RCT, adverse events included dizziness, malaise, backache, and abdominal distention requiring admission to hospital. [18] The incidence of these events was similar in the racecadotril and placebo groups (3% with racecadotril *v* 5% with placebo).

Racecadotril versus loperamide:
Reported treatment-related adverse effects were constipation, bloody stool, skin itching, and abdominal pain on palpation in one RCT. [19] The duration of abdominal distension, frequency of constipation after diarrhoea resolution, and duration of abdominal pain were higher in the loperamide group than in the racecadotril group (P = 0.1) in a second RCT. [20] The incidence of adverse events was similar between treatment groups (7% with racecadotril *v* 12% with loperamide) in a third RCT. [21] Rebound constipation was more frequent among people receiving loperamide (19%) than racecadotril (10%).

Comment:

No antibiotics were given to participants in these RCTs.

Clinical guide:
There is modest published evidence for benefit with racecadotril compared with placebo in adults; racecadotril seems to have a similar efficacy to antimotility agents in comparative trials, although there may be a lower occurrence of rebound constipation with racecadotril therapy. Safety in people with renal or hepatic diseases is not established.

OPTION ANTIBIOTICS (EMPIRICAL USE) IN RESOURCE-RICH COUNTRIES

Cure rates
Compared with placebo Antibiotics may be more effective than placebo at eradicating pathogens at 2 to 7 days (low-quality evidence).

Duration of illness
Compared with placebo Antibiotics may be more effective than placebo at reducing the duration of diarrhoea and fever in people with mild-to-moderate diarrhoea (low-quality evidence).

Symptom control
Compared with placebo Antibiotics may be more effective than placebo at reducing symptoms in people with mild-to-moderate diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

We found no systematic review but found 5 RCTs comparing empirical treatment with one or more antibiotics (ciprofloxacin, trimethoprim–sulfamethoxazole [co-trimoxazole; TMP-SMX], nifuroxazide, ofloxacin, and pefloxacin) versus placebo or symptomatic treatment. [22] [23] [24] [25] [26]

Duration of diarrhoea or fever:
The first RCT found that nifuroxazide significantly reduced mean duration of diarrhoea compared with placebo. [22] The second RCT compared three interventions: ciprofloxacin, TMP-SMX, and placebo. [23] It found that ciprofloxacin significantly shortened the duration of diarrhoea compared with placebo and found similar duration of diarrhoea with TMP-SMX and placebo in people identified as having a bacterial pathogen. The third RCT compared single-dose ofloxacin versus placebo. [24] It found no significant difference between ofloxacin and placebo in the average duration of diarrhoea, but found that ofloxacin significantly reduced duration of fever compared with placebo. The fourth RCT compared ciprofloxacin versus placebo. [25] It found that ciprofloxacin significantly reduced duration of diarrhoea and other gastrointestinal symptoms after treatment compared with placebo. The fifth RCT compared 5-day and 7-day regimens of pefloxacin versus symptomatic treatment (described as standard supportive regimen). [26] It found that both empirical pefloxacin regimens reduced the mean duration of fever days compared with symptomatic treatment. The RCT found no significant difference in the mean duration of fever days between the two pefloxacin regimens (see table 2, p 31 for all doses and full results).

Symptom control:
The first RCT found that nifuroxazide significantly reduced the number of bowel movements a day on days 1 and 2 compared with placebo, but the difference did not reach significance on day 3 of treatment. [22] The second (3-armed) RCT found that ciprofloxacin significantly increased the proportion of people cured or improved by days 1, 3, 4, and 5 compared with placebo. [23] Although TMP-SMX increased the proportion of people cured or improved compared with placebo, only the

difference on day 3 was significant. The third RCT found no significant difference in the proportion of people with unchanged symptoms for more than 48 hours between ofloxacin and placebo. [24] The fourth RCT found that ciprofloxacin significantly reduced the proportion of people with unresolved symptoms compared with placebo. [25] The fifth RCT found that both pefloxacin regimens significantly reduced the average number of loose stools a day compared with symptomatic treatment. [26] It found no significant difference in the average number of loose stools a day between the two pefloxacin regimens (see table 2, p 31 for all doses and full results).

Microbiological efficacy:
In the second RCT, 61 pathogens (mainly *Campylobacter*, *Shigella*, and *Salmonella*) were isolated from participants. [23] The RCT found that ciprofloxacin was significantly more effective in eradication of pathogens than placebo. In the third RCT, pathogens (mainly *Salmonella enteritidis*) were isolated from participants. [24] The RCT found that ofloxacin was significantly more effective in eradication of pathogens after 2 days of treatment compared with placebo. However, it found no significant difference in eradication of pathogens on day 15 with ofloxacin compared with placebo. In the fourth RCT, pathogens (mainly *Campylobacter* and *Salmonella* species) were isolated from participants. [25] The RCT found that ciprofloxacin increased the proportion of people with negative stool samples on day 5 compared with placebo. It found no significant difference in eradication of pathogens 6 weeks after treatment between the two groups. In the fifth RCT, pathogens (mainly *S enteritidis* and *Salmonella typhimurium*) were isolated from all 82 (100%) participants. [26] The RCT found that both pefloxacin regimens were significantly more effective in eradication of pathogens from day 5 onwards compared with symptomatic treatment. Both pefloxacin regimens achieved total eradication of pathogens in all people 1 week after treatment. All participants had negative stool samples 4 weeks after treatment (see table 2, p 31 for full results).

Harms: Three of the RCTs reported that no adverse effects occurred with antibiotics. [22] [24] [26] Minor adverse effects in people receiving ciprofloxacin were reported by two of the RCTs, and these included headache, myalgia, sleep disturbance, nausea, and rash. [23] [25] One of the RCTs found that, in those people with *Campylobacter* isolates, bacterial resistance occurred in 20% of people with ciprofloxacin and 21% with TMP-SMX. [23] See table 2, p 31 for full details on harms.

Comment: The pathogenic organisms isolated from people in each study varied, and may partly explain variations in effect. Reported outcomes varied between trials, which precludes direct comparisons or summaries of treatment effect.

Clinical guide:
The use of empiric antibiotic therapy should be weighed for benefits and harms.

OPTION DIET IN RESOURCE-RICH COUNTRIES

Duration of illness
Restricted diet compared with unrestricted diet Restricted diets and unrestricted diets seem to be equally effective at reducing the duration of watery and non-watery diarrhoea (moderate-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found one RCT. [27] The RCT (71 people with diarrhoea) found no significant difference in duration of watery and non-watery diarrhoea between unrestricted diet and restricted diet (watery diarrhoea, median: 14 hours with unrestricted diet *v* 13 hours with restricted diet; P = 0.46; non-watery diarrhoea, median: 18 hours with unrestricted diet *v* 42 hours with restricted diet; P = 0.15). [27] People having an unrestricted diet were instructed to eat anything they liked and drink more than normal. People having a restricted diet were instructed not to take any solid food for 24 hours and encouraged to drink more than normal.

Harms: The RCT reported nausea occurred twice as often in the unrestricted diet group (19/37 [51%] with unrestricted diet *v* 6/26 [23%] with restricted diet; P = 0.02). [27]

Comment: **Clinical guide:**
Although commonly recommended, there is limited evidence that dietary restrictions are of any benefit.

OPTION ORAL REHYDRATION SOLUTIONS IN RESOURCE-RICH COUNTRIES

We found no direct information from RCTs about the effects of oral rehydration solutions in adults with acute diarrhoea living in resource-rich countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review and no RCTs evaluating the effects of oral rehydration solutions for acute diarrhoea in adults living in resource-rich countries.

Harms: We found no RCTs.

Comment: None.

OPTION ANTIBIOTICS PLUS ANTIMOTILITY AGENTS IN RESOURCE-RICH COUNTRIES

We found no direct information from RCTs about the effects of antibiotics plus antimotility agents in adults with acute diarrhoea living in resource-rich countries. The risk of increasing bacterial resistance should be taken into account when considering the use of antibiotics.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs assessing the benefits of antibiotics plus antimotility agents in adults with acute diarrhoea living in resource-rich countries.

Harms: We found no RCTs.

Comment: **Clinical guide:**
The risk of increasing bacterial resistance should be taken into account when considering the use of antibiotics. Differences between regions in effectiveness of antibiotics are likely to be caused, in part, by local levels of antimicrobial resistance.

QUESTION What are the effects of treatments for mild-to-moderate diarrhoea in adults from resource-rich countries travelling to resource-poor countries?

OPTION ANTIMOTILITY AGENTS FOR TRAVELLERS' DIARRHOEA

Duration of illness
Loperamide hydrochloride compared with placebo Loperamide hydrochloride is more effective at reducing the duration of diarrhoea in adults with travellers' diarrhoea (moderate-quality evidence).

Loperamide hydrochloride compared with trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) Loperamide hydrochloride and TMP-SMX seem to be equally effective at reducing the duration of diarrhoea in adults with travellers' diarrhoea (moderate-quality evidence).

Compared with antimotility agents plus antibiotics Antimotility agents plus antibiotics seem to be more effective than antimotility agents alone at reducing the duration of diarrhoea in people with travellers' diarrhoea (moderate-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found two RCTs. [28] [29]

Loperamide hydrochloride versus placebo:
The first RCT (227 US school students attending summer school in Mexico, with 3 or more unformed stools in 24 hours, diarrhoea lasting 14 days or less, and at least 1 incidence of abdominal cramps, nausea, or vomiting) compared 5 interventions: loperamide hydrochloride 4 mg as loading dose and 2 mg on each loose bowel movement, single-dose trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX) 300 mg/1600 mg, TMP-SMX 160 mg/800 mg twice daily for 3 days, combination TMP-SMX 160 mg/800 mg twice daily for 3 days plus loperamide, and placebo. [28] It found that loperamide significantly reduced mean duration of diarrhoea compared with placebo (33 hours with loperamide *v* 58 hours with placebo; P less-than or equal to 0.05). Results from other arms of the RCT are presented under appropriate subheadings below. The second RCT (50 North American and Western European adult expatriates in Bangladesh, more than 3 unformed stools during previous 24 hours, and ill for <72 hours) compared loperamide 2 mg after each loose stool with placebo. [29] It found that loperamide significantly reduced the number of stools on days 1 and 2 compared with placebo (results presented graphically).

Loperamide hydrochloride alone versus TMP-SMX:
The 4-armed RCT (see above) found that the mean duration of diarrhoea was similar in both groups (33 hours with loperamide *v* 36 hours with TMP-SMX; significance not reported). [28]

Antimotility agents versus antibiotics plus antimotility agents:
See benefits of antibiotics plus antimotility agents for travellers' diarrhoea, p 13 .

Harms: The first RCT reported only one important adverse reaction, namely a self-limited rash occurring in a participant taking TMP-SMX. [28] The second RCT reported that three people treated with loperamide had dizziness, and 4 people had constipation on loperamide compared with three taking placebo (significance not reported). [29]

Antimotility agents versus antibiotics plus antimotility agents:
See harms of antibiotics plus antimotility agents for travellers' diarrhoea, p 13 .

Comment: None.

OPTION ANTIBIOTICS (EMPIRICAL USE) FOR TRAVELLERS' DIARRHOEA

Cure rates
Compared with placebo (multiple destination studies) Antibiotics seem more effective at increasing cure rates at 3 days (high-quality evidence).

Duration of illness
Compared with placebo (multiple destination studies) The antibiotics rifaximin and ciprofloxacin seem more effective at reducing the duration of diarrhoea in adults with travellers' diarrhoea (high-quality evidence).

Compared with placebo (Central America) Antibiotics seem more effective at reducing the duration of diarrhoea in adults with travellers' diarrhoea (moderate-quality evidence).

Compared with placebo (Asia) Pivemecillinam is more effective at decreasing the duration of watery stools in people with travellers' diarrhoea (moderate-quality evidence).

Antibiotics compared with each other (multiple destination studies) Norfloxacin and trimethoprim–sulfamethoxazole (co-trimoxazole) seem to be equally effective at reducing the duration of diarrhoea in people with travellers' diarrhoea (moderate-quality evidence).

Compared with each other (Central America) Furazolidone may be as effective as ampicillin at reducing the duration of illness in people with travellers' diarrhoea (low-quality evidence).

Compared with each other (Asia) Azithromycin and ciprofloxacin may be equally effective at decreasing the duration of illness in people with travellers' diarrhoea (low-quality evidence).

Symptom control
Compared with placebo (North and West Africa) Fleroxacin may be more effective at producing stools of normal consistency, at increasing the number of people with total relief of diarrhoea, and at curing all symptoms (low-quality evidence). 1-day and 2-day fleroxacin regimens may be equally effective at increasing the number of people cured of all symptoms (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found one systematic review (search date 2003, 19 RCTs, 3157 people), [30] and two subsequent RCTs [31] [32] comparing a variety of antibiotics versus placebo, a different dose of the same antibiotic, or another antibiotic, in adults travelling from resource-rich countries to resource-poor countries.

Antibiotics (empirical) versus placebo:
Multiple destination studies (Central America, South America, Africa):

The systematic review [30] identified one RCT, [33] and we found two subsequent RCTs. [31] [32] The RCT identified by the review (447 Swedish travellers to Africa, Asia, or Latin America with acute diarrhoea) compared oral norfloxacin (400 mg twice daily for 3 days) versus placebo. [33] It found that norfloxacin significantly increased cure rates for diarrhoea after 3 days (1 or less loose stools/24 hours without additional symptoms) compared with placebo (34/48 [74%] with norfloxacin *v* 18/48 [38%] with placebo; P <0.0001). The first subsequent RCT (380 adult tourists in Guatemala, Mexico, and Kenya with acute diarrhoea defined as 3 or more unformed stools in 24 hours plus 1 additional sign of enteric infection) compared three interventions; rifaximin (600 mg/day for 3 days), rifaximin (1200 mg/day for 3 days), and placebo. [31] At 5 days' follow-up, rifaximin 600 mg/day and rifaximin 1200 mg/day significantly reduced median time since last unformed stool compared with placebo (32.5 hours with rifaximin 600 mg/day *v* 32.9 hours with rifaximin 1200 mg/day *v* 60.0 hours with placebo; P = 0.0001 for either rifaximin group *v* placebo). The second subsequent RCT (399 travellers to Mexico, Guatemala, India, or Peru) was a three-arm trial comparing rifaximin (200 mg 3 times a day) versus ciprofloxacin (500 mg twice daily plus placebo once daily) versus placebo (3 times daily). [32] It found that both rifaximin and ciprofloxacin significantly reduced the

duration of diarrhoea compared with placebo (median time to last unformed stool: 32 hours with rifaximin *v* 65.5 hours with placebo; P <0.001; 28.8 hours with ciprofloxacin *v* 65.5 hours with placebo; P <0.0003; intention-to-treat analysis).

Central America (Mexico, Belize):

We found one systematic review, [30] which identified 11 RCTs. [28] [34] [35] [36] [37] [38] [39] [40] [41] [42] [43] The second and third RCTs compared ciprofloxacin versus placebo. Both RCTs found that ciprofloxacin significantly reduced duration of illness compared with placebo (see table 3, p 33). [34] [35] The other 8 RCTs were all carried out in the same centre in Guadalajara, Mexico, and are described in table 3, p 33 . Eight RCTs found that antibiotics significantly reduced the duration of illness compared with placebo. [28] [36] [37] [39] [40] [41] [42] [43]

North and West Africa (Morocco, Egypt, the Gambia):

We found one RCT (195 tourists in the Gambia with acute diarrhoea, defined as 1 or more watery or soft stool plus abdominal cramps, vomiting, or nausea), which compared three interventions: fleroxacin (400 mg for 1 day), fleroxacin (400 mg/day for 2 days), and placebo. [44] It found that both 1-day and 2-day fleroxacin were significantly more effective than placebo in producing normal stool consistency at 48 hours' follow-up (36/54 [67%] with 1 day *v* 34/48 [71%] with 2 day *v* 18/49 [37%] with placebo; P <0.01 for either dose of fleroxacin *v* placebo). It found no significant difference between different doses of fleroxacin (P value not reported). Both doses of fleroxacin significantly increased the proportion of people with total relief of diarrhoea compared with placebo, but there was no significant difference between different doses of fleroxacin (36 hours: 50% with 1 day *v* 50% with 2 days *v* 14% with placebo; 48 hours: 67% with 1 day *v* 71% with 2 days *v* 37% with placebo; absolute numbers not reported; P <0.05 between fleroxacin groups *v* placebo; no significant difference between different doses of fleroxacin; P value not reported). Fleroxacin at either dose significantly increased the proportion of people cured of all symptoms compared with placebo, but there was no significant difference between different doses of fleroxacin (48 hours: 28/54 [52%] with 1 day *v* 24/48 [50%] with 2 days *v* 14/49 [29%] with placebo; P <0.05 between fleroxacin groups *v* placebo; no significant difference between fleroxacin at different doses; P value not reported; 72 hours: >80% with 1 day *v* >80% with 2 days *v* 47% with placebo; absolute numbers not reported; P <0.01 between fleroxacin groups *v* placebo; no significant difference between fleroxacin groups; P value not reported).

Asia (India, Thailand):

We found one systematic review, [30] which identified one RCT. [45] The RCT (47 Danish tourists with diarrhoea in India) compared pivmecillinam (400 mg 3 times daily for 3 days) versus placebo. It found that pivmecillinam significantly reduced the duration of watery stools compared with placebo (<24 hours' duration: 20/24 [83%] with pivmecillinam *v* 10/23 [43%] with placebo; 24–48 hours' duration: 6/24 [25%] with pivmecillinam *v* 8/23 [35%] with placebo; more than 48 hours' duration: 0/24 [0%] with pivmecillinam *v* 6/23 [26%] with placebo; P <0.05). [45]

Antibiotics (empirical) versus each other:
Multiple destination studies (Central America, South America, Africa):

We found one systematic review, [30] which identified one RCT. [46] The RCT (142 US male military personnel in South America and West Africa with acute diarrhoea) compared oral norfloxacin (400 mg twice daily for 5 days) versus oral trimethoprim–sulfamethoxazole (co-trimoxazole, TMP-SMX; 160 mg/800 mg twice daily for 5 days). [46] It found no significant difference in duration of diarrhoea between norfloxacin and TMP-SMX (mean number of days of diarrhoea after beginning treatment: 1.6 with norfloxacin *v* 1.8 with TMP-SMX; P = 0.37). Bacterial enteropathogens in stool samples were identified in 36/73 (49%) of the norfloxacin group and 27/69 (39%) of the TMP-SMX group. In vitro resistance was found to TMP-SMX in 20/74 (27%) of isolates tested but not to norfloxacin. [46]

Central America (Mexico, Belize):

One RCT found no significant difference in duration of illness between furazolidone and ampicillin. [38]

North and West Africa (Morocco, Egypt, The Gambia):

We found one systematic review, [30] which identified one RCT, [44] comparing 1-day versus 2-day fleroxacin versus placebo. It found a significant difference in the proportion of people cured of all symptoms between different doses of fleroxacin (48 hours: 28/54 [52%] with 1 day *v* 24/48 [50%]

with 2 days; P value not reported, reported as not significant; 72 hours: >80% with 1 day *v* >80% with 2 days; absolute numbers and P value not reported; reported as not significant).

Asia (India, Thailand):

We found one systematic review, [30] which identified one RCT. [47] The RCT (79 US military personnel in Thailand with acute diarrhoea, defined as 3 or more liquid bowel movements in 24 hours or 2 liquid movements plus fever, cramps, nausea, or vomiting) compared azithromycin 500 mg versus ciprofloxacin 500 mg. It found that mean duration of illness was similar in both groups (36.9 hours with azithromycin *v* 38.2 hours with ciprofloxacin; reported as similar; P value not reported). [47]

Antibiotics versus antibiotics plus antimotility agents:
See benefits of Antibiotics plus antimotility agents for travellers' diarrhoea, p 13 .

Harms:

Antibiotics (empirical) versus placebo:
The systematic review [30] conducted a meta-analysis of 5 RCTs. [36] [37] [42] [43] [44] There were significantly more adverse effects in people taking antibiotics compared with placebo (OR 2.37, 95% CI 1.50 to 3.75). However, the adverse effects were not serious and resolved on withdrawal from the drug.

Multiple destination studies (Latin America, South America, Africa):

The RCT included in the review [30] reported two adverse events with norfloxacin (constipation, heartburn: 2/19 [11%]) and 7 adverse events in the placebo group (vertigo, headache, myalgia, constipation, and paraesthesia: 7/21 [33%]). [33] None of the people had norfloxacin-resistant *Escherichia coli* before or after treatment; however, *E coli* resistant to other antibiotics was more frequent after treatment, particularly in the placebo group. The first subsequent RCT found no significant difference in non-serious adverse events (gastrointestinal-related, headache) between groups (74/125 [59.2%] with rifaximin 600 mg *v* 88/126 [69.8%] with rifaximin 1200 mg *v* 90/129 [69.7%] with placebo). [31] Fatigue was reported significantly more with rifaximin 1200 mg (P = 0.023; absolute data not reported). The second subsequent RCT reported a similar rate of adverse events among the three groups. The most common adverse event was headache. There were no early withdrawals because of treatment-related adverse events in the rifaximin or placebo groups (no further information reported). [32]

Central America (Mexico, Belize):

See table 3, p 33 for details of the adverse effects of treatment. [28] [34] [35] [36] [37] [38] [39] [40] [42] [43] Overall, these RCTs found that adverse effects with antibiotics were mild and self-limiting.

North and West Africa (Morocco, Egypt, the Gambia):

The RCT (106 people) reported more mild adverse effects with placebo than with norfloxacin (7 cases with norfloxacin *v* 18 cases with placebo; significance not reported). [48] The second RCT (safety analysis on 190/195 people), found that adverse effects judged to be remotely, possibly, or probably related to the treatment were significantly more likely with 1-day fleroxacin or 2-day fleroxacin compared with placebo (36/61 [59%] with 1 day *v* 42/65 [65%] with 2 day *v* 25/64 [39%] with placebo; P <0.05 for either dose *v* placebo). [44] The most common adverse event was fatigue. No adverse event was considered to be serious.

Asia (India, Thailand):

The RCT did not report on adverse effects. [45]

Antibiotics (empirical) versus each other:
Multiple destination studies (Latin America, South America, Africa):

The first RCT stated that no adverse effects were reported. [46] The second subsequent RCT reported a similar rate of adverse events among the three groups. The most common adverse event was headache. There were no early withdrawals because of treatment-related adverse events in the rifaximin group (no further information reported). [32]

North and West Africa (Morocco, Egypt, the Gambia):

The RCT (safety analysis on 190/195 people), found that adverse effects judged to be remotely, possibly, or probably related to the treatment, were more likely in the 2-day fleroxacin than 1-day fleroxacin group (42/65 [65%] with 2 day *v* 36/61 [59%] with 1 day; P value and significance not

reported). [44] The most common adverse event was fatigue. No adverse event was considered to be serious.

Asia (India, Thailand):

The RCT did not report on adverse effects. [47]

Antibiotics versus antibiotics plus antimotility agents:
See harms of Antibiotics plus antimotility agents for travellers' diarrhoea, p 13 .

Comment:

We found one RCT (598 people aged 12 years and under with acute diarrhoea lasting 5 days or less; only 70% of people had travellers' diarrhoea, the rest had non-travellers' diarrhoea) comparing norfloxacin 400 mg twice daily versus placebo. [49] It found that norfloxacin significantly increased the proportion of people who were cured (1 loose stool or less/24 hours without additional symptoms) after 5 days compared with placebo (161/257 [63%] with norfloxacin *v* 130/254 [51%] with placebo; P = 0.003).

Clinical guide:
Evidence supports the use of antibiotics in travellers with diarrhoea. Differences in effectiveness of antibiotics between regions are likely to be caused by local levels of antimicrobial resistance. As the prevalence of resistance steadily changes, it would be misleading to ascribe differences in efficacy to location.

OPTION ANTIBIOTICS PLUS ANTIMOTILITY AGENTS FOR TRAVELLERS' DIARRHOEA

Cure rates
Compared with antibiotics alone Antibiotics plus loperamide may be more effective than antibiotics alone at increasing the proportion of people with clinical cure at 24 hours and 48 hours in people with travellers' diarrhoea, but not at 72 hours (low-quality evidence).

Duration of illness
Compared with antibiotics alone Antibiotics plus loperamide may be more effective than antibiotics alone at reducing the time to the last unformed stool in people with travellers' diarrhoea. However, results varied widely depending on the regimen used (low-quality evidence).

Compared with antimotility agents alone Antibiotics plus antimotility agents seem to be more effective at reducing the duration of diarrhoea in people with travellers' diarrhoea (moderate-quality evidence).

Different antibiotics plus antimotility agent regimens compared with each other We don't know whether a single dose of ciprofloxacin plus loperamide is more effective than loperamide plus ciprofloxacin taken for 3 days at decreasing the time to last unformed stool or at decreasing the mean number of liquid stools at 24 to 48 hours in people with travellers' diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

Antibiotics plus antimotility agents versus antibiotics alone:
We found one systematic review (search date 2007), which compared antibiotic plus loperamide versus the same antibiotic alone. [50] Antibiotics used included trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX), ciprofloxacin, ofloxacin, and azithromycin. The review reported that the average age of participants ranged from 23 to 27 years, and although eligibility criteria varied with regard to fever and allowable symptom duration, all RCTs excluded people with dysenteric stools (bloody, mucoid, or both, stools). Clinical cure varied slightly among studies, but generally included resolution of loose stools and symptoms (fever, nausea, vomiting, cramps, myalgia, orthostatic hypotension, or a combination). The review found that antibiotic plus loperamide significantly increased clinical cure at 24 and 48 hours compared with antibiotic alone (24 hours: 6 RCTs; OR 2.58, 95% CI 1.84 to 3.61; 48 hours: 6 RCTs; OR 2.15, 95% CI 1.50 to 3.09; absolute numbers not reported for either analysis). [50] It found no significant difference in clinical cure between groups at 72 hours (5 RCTs; OR 1.40, 95% CI 0.91 to 2.14; absolute numbers not reported). [50] Included RCTs ranged in size from 104 to 310 people. The review reported that 5 RCTs all found that antibiotic plus loperamide significantly improved the time to last unformed stool compared with antibiotic alone (range in individual RCTs: shortest improvement, WMD –2 hours, 95% CI –0.3 hours to –3.7 hours; largest improvement, WMD –23 hours, 95% CI –21.5 hours to –24.5 hours; results presented graphically, absolute numbers not reported), but noted that there was significant heterogeneity among RCTs (P <0.001) and did not pool data for this comparison. [50] The review did not explain the heterogeneity. Antibiotic regimens varied between RCTs with three RCTs using a single-dose regimen and three RCTs using a 3-day regimen. Of the included studies, 4 RCTs were in US student

travellers to Mexico, and two RCTs were in US military populations (1 RCT in Egypt and 1 RCT in Thailand).

Antibiotics plus antimotility agents versus antimotility agents alone:
We found no systematic review but found one RCT. [28] The RCT (227 US students travelling in Mexico) found that TMP-SMX plus loperamide significantly reduced mean duration of diarrhoea (time to last unformed stool) compared with loperamide alone. [28] See table 4, p 35 .

Different antibiotics plus antimotility agent regimens versus each other:
We found no systematic review but found one RCT. [51] The RCT (142 US soldiers deployed in Thailand who developed diarrhoea) found no significant difference in the proportion of people fully recovered at 24, 48, and 72 hours between ciprofloxacin single dose plus loperamide compared with ciprofloxacin for 3 days plus loperamide. It also found no significant difference between groups in mean time until the last unformed stool, or mean time until all symptoms were relieved. [51] See table 4, p 35 .

Harms:

Antibiotics plus antimotility agents versus antibiotics alone:
The systematic review that compared antibiotic plus loperamide versus the same antibiotic alone did not report on harms. [50]

Antibiotics plus antimotility agents versus antimotility agents alone:
The RCT [28] reported on adverse effects; for details see harms of antimotility agents for travellers' diarrhoea, p 9 .

Different antibiotics plus antimotility agent regimens versus each other:
The RCT gave no information on adverse effects. [51]

Comment:

The predominant pathogens found in the RCTs were different, with enterotoxigenic *E coli* being the predominant identified pathogen in the studies in Mexico and Egypt. Exploratory analyses in some of the studies suggested that the combination was most effective for enterotoxigenic *E coli*, but not for *Shigella*, *Salmonella*, or other invasive or cytopathic pathogens.

Clinical guide:
The evidence seems to be in favour of antibiotic/loperamide combination therapy over antibiotics alone, effecting increased clinical cure rates at 24 and 48 hours. This effect is, however, variable across different antibiotics, with uncertain benefit for individual agents, and may further be related to the pathogens encountered.

Antimotility agents are not recommended for people with suspected shigellosis or Shiga-toxin-producing *E coli*. [1]

OPTION BISMUTH SUBSALICYLATE FOR TRAVELLERS' DIARRHOEA

Duration of illness
Compared with placebo Bismuth subsalicylate is more effective at reducing the duration of diarrhoea (high-quality evidence).

Compared with loperamide Bismuth subsalicylate is less effective at reducing the time to last unformed stool (high-quality evidence).

Symptom control
Compared with placebo Bismuth subsalicylate seems to be more effective at reducing the number of loose stools at 4 to 24 hours after treatment (moderate-quality evidence).

Compared with loperamide Bismuth subsalicylate is less effective at reducing the number of unformed stools at 0 to 48 hours (high-quality evidence).

Note
The modest benefits of bismuth subsalicylate may be outweighed by large and frequent doses of the liquid preparation needed. Bismuth subsalicylate is associated with frequent minor adverse effects such as black tongue or black stools.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

We found no systematic review but found 4 RCTs of treatment of acute diarrhoea with bismuth subsalicylate compared with placebo or loperamide. [52] [53] [54] [55]

Bismuth subsalicylate versus placebo:
We found two RCTs. [52] [53] The first RCT (111 US students attending a Mexican university who developed diarrhoea) compared bismuth subsalicylate versus placebo. Students with three or four unformed stools in the preceding 24 hours received bismuth subsalicylate 30 mL every 30 minutes for 8 doses; those with 5 or more unformed stools in 24 hours received 60 mL every 30 minutes for 8 doses. The RCT found that both doses of bismuth subsalicylate significantly reduced the number of loose stools compared with placebo at 4 to 24 hours after treatment (109 with bismuth subsalicylate 30 mg *v* 165 with placebo; P <0.05; 39 with bismuth subsalicylate 60 mg *v* 77 with placebo; P <0.05). [52] The second RCT (133 Europeans visiting West Africa and 112 American students in Mexico who had travellers' diarrhoea) compared bismuth subsalicylate 1050 mg suspension versus placebo every hour up to 4 doses a day for 2 days for the West African study, and bismuth subsalicylate 525 mg versus placebo every 30 minutes up to 8 doses a day for 2 days for the Mexican study. [53] The RCT found that bismuth subsalicylate significantly reduced the duration of diarrhoea compared with placebo in both sites (West Africa: 25.8 hours with bismuth subsalicylate *v* 34.5 hours with placebo; P <0.01; Mexico: 24.2 hours bismuth subsalicylate *v* 31.4 hours with placebo; P = 0.02).

Bismuth subsalicylate versus loperamide:
We found two RCTs. [54] [55] The first RCT (219 students with acute diarrhoea while visiting 7 countries in Latin America) compared bismuth subsalicylate 30 mL every 30 minutes for 8 doses for 2 days versus loperamide 4 mg followed by 2 mg after each unformed stool. [54] The RCT found that bismuth subsalicylate was significantly less effective at reducing the number of unformed stools at 0 to 48 hours compared with loperamide (0–4 hours: 1.3 with bismuth subsalicylate *v* 0.9 with loperamide; P <0.0004; 4–24 hours: 2.4 with bismuth subsalicylate *v* 1.5 with loperamide; P <0.002; 24–48 hours: 1.0 with bismuth subsalicylate *v* 0.8 with loperamide; P <0.05). [54] The number who received rescue treatment with antimicrobial drugs (trimethoprim–sulfamethoxazole [co-trimoxazole; TMP-SMX]) was similar between groups (28% with bismuth subsalicylate *v* 24% with loperamide; absolute numbers not reported). [54] The second RCT (203 students in Mexico) compared bismuth subsalicylate 35 mL (612.5 mg) every 30 minutes up to 8 doses versus loperamide liquid 20 mL (4 mg) followed by 2 mg after each unformed stool. [55] The RCT found that bismuth subsalicylate was significantly less effective at reducing time to last unformed stool compared with loperamide (median: 13.9 hours with bismuth subsalicylate *v* 3.4 hours with loperamide; P = 0.001). [55]

Harms:

Bismuth subsalicylate versus placebo:
The first RCT gave no information on adverse effects. [52] The second RCT reported that the main adverse reactions noted among people treated with bismuth subsalicylate were black tongue (22% with bismuth subsalicylate *v* 4% with placebo) and black stools (69% with bismuth subsalicylate *v* 11% with placebo). [53]

Bismuth subsalicylate versus loperamide:
The first RCT reported that in the bismuth subsalicylate group, two people complained of tinnitus, three became nauseated after taking medication, one had dizziness, and one became constipated. In the loperamide group, 8 people complained of constipation, 4 experienced headache, and two had drowsiness and dizziness. [54] The second RCT reported that adverse effects were minimal, equally distributed between treatments, and for the most part indistinguishable from the symptoms commonly associated with diarrhoeal syndrome. [55]

Comment:

Clinical guide:
There is evidence that bismuth is more effective than placebo, but less effective than loperamide. However, given the modest benefit and the frequent dosing and large volume required if using the liquid formulation, bismuth is a little-used clinical treatment option.

OPTION ANTISECRETORY AGENTS FOR TRAVELLERS' DIARRHOEA

Duration of illness
Zaldaride maleate compared with placebo High doses of zaldaride maleate may be more effective at reducing the time to passage of last unformed stool, but may be associated with cardiovascular symptoms (low-quality evidence).

Zaldaride maleate compared with loperamide Zaldaride maleate is less effective at reducing the mean number of unformed stools at 48 hours (moderate-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found two RCTs of antisecretory agents among travellers. [56] [57]

Zaldaride maleate versus placebo:
One RCT (176 adult American students who developed acute diarrhoea while visiting Mexico) compared three doses of zaldaride maleate versus placebo. [56] Participants received zaldaride maleate 5 mg, 10 mg, or 20 mg, or placebo 4 times daily for 2 days. The RCT found no significant difference in time for passage of last unformed stool between zaldaride maleate (5 mg or 10 mg) and placebo (median: 41.5 hours with zaldaride maleate 5 mg *v* 40.8 hours zaldaride maleate 10 mg *v* 42.5 hours with placebo, reported as not significant; P values not reported). However, the time to passage of last unformed stool was significantly shorter with zaldaride maleate 20 mg compared with placebo (median: 20.0 hours with zaldaride maleate 20 mg *v* 42.5 hours with placebo; P <0.01). [56]

Zaldaride maleate versus loperamide versus placebo:
We found one RCT (179 adult American students travelling to Mexico who developed diarrhoea of <4 days' duration) comparing zaldaride maleate versus loperamide. [57] People were randomised to zaldaride maleate (20 mg 4 times daily), loperamide (4 mg followed by 2 mg after each unformed stool), or placebo. The RCT found that zaldaride maleate was significantly less effective than loperamide in reducing the mean number of unformed stools during 48 hours (mean: 5.56 with zaldaride maleate *v* 2.74 with loperamide; P <0.0005). The RCT also found that both zaldaride maleate and loperamide significantly shortened duration of diarrhoea compared with placebo (median: 34.5 hours with zaldaride maleate *v* 45 hours with placebo; P = 0.034; median: 24 hours with loperamide *v* 45 hours with placebo; P <0.001). [57]

Harms: The first RCT found 16 people with adverse effects, including headache, dizziness, chest pressure, and numbness in fingers and toes. [56] The second RCT reported headache as the most common adverse effect, and it occurred in similar proportions in the three study groups. [57]

Comment: Further development of zaldaride maleate has been halted because of concerns over cardiovascular symptoms related to higher doses.

OPTION DIET FOR TRAVELLERS' DIARRHOEA

Duration of illness
Restricted diet compared with unrestricted diet We don't know whether restricted diets are more effective at reducing the duration of diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found one RCT comparing restricted versus unrestricted diet. [58] The RCT (105 US college students in Guadalajara) found no significant difference in duration of diarrhoea for students on a restricted diet versus students on an unrestricted diet (mean: 37 hours with restricted diet *v* 33 hours with unrestricted diet; P = 0.59). [58] Adherence to both interventions was good. The students were part of studies investigating the effect of antibiotics on travellers' diarrhoea, and all received one of 4 antibiotics (levofloxacin, azithromycin, rifaximin, or ciprofloxacin). Participants were grouped to the same intervention according to the household in which they resided during their stay.

Harms: The RCT gave no information on adverse effects. [58]

Comment: None.

Clinical guide:
Although commonly recommended, there is limited evidence that dietary restrictions are of any benefit.

OPTION ORAL REHYDRATION SOLUTIONS FOR TRAVELLERS' DIARRHOEA

We found no direct information from RCTs about the effects of oral rehydration solutions on acute mild-to-moderate diarrhoea in adults from resource-rich countries travelling to resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs.

Harms: We found no RCTs.

Comment: One RCT (80 US students in Mexico) compared oral rehydration solution (500 mL initially, followed by 250 mL after each unformed stool, up to 1000 mL/day) plus loperamide (4 mg initially, followed

by 2 mg after each unformed stool, up to 8 mg/day) versus loperamide alone for 48 hours. [59] It found no significant difference between groups in duration of diarrhoea or symptom control.

Clinical guide:
Most clinicians believe that oral rehydration solution is the first-line of treatment for diarrhoea.

QUESTION **What are the effects of treatments for mild-to-moderate diarrhoea in adults living in resource-poor countries?**

OPTION **ANTIMOTILITY AGENTS FOR MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES**

Symptom control
Compared with placebo Lidamidine may be more effective at reducing the number of loose stools at 72 hours and mean stool weight at 29 hours in adults with acute diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

Antimotility agents versus placebo:
We found no systematic review, but found two RCTs from Mexico comparing antimotility agents versus placebo, versus each other, or comparing different doses of the same antimotility drug. [60] [61] The first RCT (30 adults with acute diarrhoea) found that lidamidine (2 mg or 4 mg) reduced the mean stool weight after 29 hours compared with placebo (435 g with lidamidine 4 mg *v* 364 g with lidamidine 2 mg *v* 576 g with placebo; P value not reported). [60] The second RCT (105 adults with acute diarrhoea) compared three interventions: lidamidine, loperamide, and placebo. [61] It found that people had fewer loose stools with lidamidine over 72 hours compared with placebo (mean stools per person: 3.9 with lidamidine *v* 8.5 with placebo; P value not reported).

Harms:

The first RCT reported that lidamidine was associated with infrequent mild adverse effects (proportion affected not reported). These included sleep disturbance, abdominal pains, and nausea. [60] The second RCT reported that abdominal pain occurred in a similar number of people with loperamide and placebo (5/35 [14%] with loperamide *v* 4/35 [11%] with placebo; proportion affected with lidamidine and significance of difference not reported). The RCT reported that two people taking loperamide developed constipation and bloating, and one person taking lidamidine developed constipation. [61]

Comment:

Clinical guide:
There is evidence of benefit for antimotility agents. However, these agents are not recommended for patients with suspected shigellosis or Shiga-toxin-producing *E coli*. [1]

OPTION **ANTISECRETORY AGENTS FOR MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES**

Duration of illness
Racecadotril compared with loperamide Racecadotril and loperamide seem to be equally effective at reducing the duration of diarrhoea (high-quality evidence).

Note
Racecadotril has been associated with fewer adverse effects compared with loperamide, particularly rebound constipation.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

We found no systematic review but found one RCT. [62]

Racecadotril (acetorphan) versus loperamide:
We found one RCT (945 adults living in 14 resource-poor countries with acute diarrhoea) comparing racecadotril 100 mg twice daily versus loperamide 2 mg twice daily until resolution of diarrhoea. [62] The RCT found no significant difference in the median duration of diarrhoea between groups (55 hours, 95% CI 50 hours to 65 hours, with racecadotril *v* 55 hours, 95% CI 48 hours to 66 hours, with loperamide). [62]

Harms:

The RCT found that that 44 people (9%) taking racecadotril and 87 (18%) taking loperamide had adverse experiences that were related to treatment. Adverse effects occurring in >1% of the study population included constipation, enlarged abdomen, anorexia, headache, and abdominal pain (constipation: 3% with racecadotril *v* 13% with loperamide; enlarged abdomen: 2% with racecadotril

v 6% with loperamide; anorexia: 1% with racecadotril *v* 2% with loperamide; headache: 2% with racecadotril *v* 0.4% with loperamide; abdominal pain: 0.2% with racecadotril *v* 2% with loperamide). [62]

Comment: **Clinical guide:**
Racecadotril seems to have similar efficacy in adults compared to loperamide, possibly with fewer adverse effects.

OPTION ANTIBIOTICS (EMPIRICAL USE) FOR MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Symptom control
Compared with placebo We don't know whether antibiotics are more effective at reducing the number of unformed stools passed or at increasing the number of people who are well by 72 hours in people with acute mild-to-moderate diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review but found one article reporting two RCTs from Mexico that compared two different antibiotics versus placebo and versus trimethoprim–sulfamethoxazole (co-trimoxazole; TMP-SMX). [63] The first RCT (307 adults with 3 or more unformed stools in 24 hours, of less than 72 hours' duration and, if pre-treatment, stools contained 10 or more fecal leukocytes per high-powered field microscopically) compared TMP-SMX 160 mg/800 mg twice daily versus clioquinol 250 mg three times daily versus placebo. The RCT found no significant difference in mean number of unformed stools passed during the 3-day study (4.2 with TMP-SMX *v* 4.2 with clioquinol *v* 5.3 with placebo; P value not reported). Analysis was not intention to treat (20 [7%] people were excluded from the analysis). The second RCT (150 men with 4 or more unformed stools in the previous 24 hours, or 3 unformed stools in the previous 8 hours and 1 or more incidences of fever, abdominal pain, fecal urgency, nausea, or vomiting of no more than 60 hours' duration) compared three interventions: enoxacin, TMP-SMX, and placebo. It found no significant difference in the proportion of people who were well by 72 hours with enoxacin, TMP-SMX, or placebo (23/47 [49%] with enoxacin *v* 21/43 [49%] with TMP-SMX *v* 16/49 [33%] with placebo; P >0.05). [63] Analysis was not intention to treat (13 [9%] people were excluded from the analysis). Results were separated out into subgroups on the basis of presence of pathogens before statistical analysis.

Harms: The first RCT did not report on adverse effects. [63] The second RCT reported that 4 people had adverse effects leading to removal from the trial (one with light-headedness, vertigo, and photophobia and one with moderate depression in the enoxacin group; and one person with skin rash and one with moderate nervousness and abdominal pain in the TMP-SMX group).

Comment: **Clinical guide:**
Use of empiric antibiotic therapy should be weighed for benefits and harms.

OPTION ANTIBIOTICS PLUS ANTIMOTILITY AGENTS FOR MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES

We found no direct information from RCTs about antibiotics plus antimotility agents in adults with acute mild-to-moderate diarrhoea living in resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs assessing antibiotics plus antimotility agents in adults with acute mild-to-moderate diarrhoea living in resource-poor countries.

Harms: We found no RCTs.

Comment: None.

OPTION ORAL REHYDRATION SOLUTIONS FOR MILD-TO-MODERATE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Symptom control
Citrate oral rehydration solution compared with bicarbonate oral rehydration solution We don't know whether citrate oral rehydration solutions are more effective at reducing stool output at 48 hours in adults with acute uncomplicated diarrhoea (low-quality evidence).

Commercial oral rehydration solution compared with standard oral rehydration solution We don't know whether two commercially available sports drinks and standard oral rehydration solution differ in effectiveness at reducing stool frequency or weight as we found insufficient evidence from one small RCT (very low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

Citrate oral rehydration solution (ORS) versus bicarbonate ORS:
We found no systematic review but found one RCT comparing citrate ORS versus bicarbonate ORS. [64] The RCT (57 adults in Bangladesh with acute uncomplicated diarrhoea) found no significant difference between treatments in stool output from baseline to 24 hours, or from 24 hours to 48 hours (from 0 to 24 hours: 41.5 mL/kg with citrate ORS *v* 34.9 mL/kg with bicarbonate ORS; reported as not significant; from 24 to 48 hours: 30.3 mL/kg with citrate ORS *v* 26.6 mL/kg with bicarbonate ORS; reported as not significant). Three people from the citrate group and 4 people from the bicarbonate ORS group were excluded, mainly as they were unable to be rehydrated orally because of persistent vomiting.

Commercial ORS versus standard ORS :
We found one RCT (75 adults with acute viral diarrhoea and mild dehydration [>8 stools per day, 5% or less dehydration], inpatients in a community hospital in India), which compared rehydration with commercial sports drinks (Gatorade or Pedialyte) versus standard ORS. [65] Results were based on 60/75 (80%) people who completed the study. The RCT reported that there was no difference between groups in stool frequency and that stool weight was similar at 24 to 48 hours (no statistical analysis between groups reported, results presented graphically, absolute data not reported for either group). [65]

Harms:

Citrate oral rehydration solution (ORS) versus bicarbonate ORS:
The RCT gave no information on adverse effects. [64]

Commercial ORS versus standard ORS:
The RCT did not report on harms. [65]

Comment:

Clinical guide:
Most clinicians believe that oral rehydration solution is the first-line treatment for diarrhoea.

QUESTION What are the effects of treatments for severe diarrhoea in adults living in resource-poor countries?

OPTION ANTIBIOTICS (EMPIRICAL USE) FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

We found no direct information from RCTs about the empirical use of antibiotics in treating severe diarrhoea in adults living in resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review and no RCTs evaluating the effects of empirical use of antibiotics in treating severe diarrhoea in adults living in resource-poor countries.

Harms: We found no RCTs.

Comment: See comment under oral rehydration solutions, p 18 .

OPTION ANTIMOTILITY AGENTS FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

We found no direct information from RCTs about antimotility agents in treating severe diarrhoea in adults living in resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs evaluating the effects of antimotility agents in treating severe diarrhoea in adults living in resource-poor countries.

Harms: We found no RCTs.

Comment: None.

OPTION ANTIBIOTICS PLUS ANTIMOTILITY AGENTS FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness

Antibiotics plus antimotility agents compared with antibiotics Antibiotics plus antimotility agents are more effective at reducing the duration of diarrhoea and daily number of diarrhoeal stools in people with dysentery caused by the invasive bacterial pathogens Shigella or enteroinvasive Escherichia coli, but the combination seems no more effective than antibiotics alone in people infected with pathogens other than Shigella or enteroinvasive E coli (moderate-quality evidence).

Note

Antimotility agents are not recommended for people with suspected shigellosis or Shiga-toxin-producing E coli.

For GRADE evaluation of interventions for diarrhoea in adults (acute), **see table, p 37 .**

Benefits:

Antibiotics plus antimotility agents versus antibiotics plus placebo:
We found no systematic review but found one small RCT (88 adults admitted to hospital with dysentery in Thailand), comparing ciprofloxacin 500 mg twice daily for 3 days plus loperamide (4 mg initial dose plus 2 mg after each loose stool) versus ciprofloxacin 500 mg twice daily for 3 days plus placebo. [66] The RCT did not report results for all participants together; instead, results were reported for those found to have invasive bacterial pathogens (*Shigella* or enteroinvasive *E coli*) separately. The RCT found that, for people with invasive bacterial pathogens, ciprofloxacin plus loperamide significantly reduced duration of diarrhoea and daily number of diarrhoeal stools (median duration: 19 hours with ciprofloxacin plus loperamide *v* 42 hours with placebo; P = 0.028; median daily number of diarrhoeal stools: 2 with ciprofloxacin plus loperamide *v* 6.5 with placebo; P = 0.016). However, it found no significant difference between groups among people infected with other organisms (median duration of diarrhoea: 42 hours with ciprofloxacin plus loperamide *v* 43 hours with placebo; P = 0.99; median daily number of diarrhoeal stools: 6 with ciprofloxacin plus loperamide *v* 7.5 with placebo; P = 0.41). [66] Pathogens identified in the stool samples of this group included *Vibrio parahaemolyticus*, *Campylobacter jejuni*, and *Entamoeba histolytica*; some people had no pathogen, or multiple pathogens identified.

Harms:

Antibiotics plus antimotility agents versus antibiotics plus placebo:
The RCT reported that combination treatment was not associated with prolonged duration of fever and that no adverse effects were detected (further data not reported). [66]

Comment:

Clinical guide:
Despite the above findings, antimotility agents are not recommended for people with suspected shigellosis or Shiga-toxin-producing *E coli*; therefore, combination treatment would not generally be used in clinical practice. [1]

OPTION ANTISECRETORY AGENTS FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness

Racecadotril compared with placebo Racecadotril is no more effective at reducing the duration of diarrhoea in people with acute diarrhoea associated with severe dehydration (moderate-quality evidence).

Berberine compared with placebo/no treatment Berberine may be no more effective at reducing the duration of diarrhoea in people with non-cholera diarrhoea (low-quality evidence).

Berberine plus tetracycline compared with tetracycline alone Berberine plus tetracycline may be more effective at reducing the duration of diarrhoea in people with cholera (low-quality evidence).

Chlorpromazine compared with no treatment Chlorpromazine may be more effective at reducing the duration of diarrhoea in people with severe dehydration due to diarrhoea (very low-quality evidence).

Symptom control

Racecadotril compared with placebo Racecadotril is no more effective at reducing mean total stool output or mean total rehydration solution intake in people with acute diarrhoea associated with severe dehydration (moderate-quality evidence).

Berberine compared with placebo/no treatment Berberine may be more effective at reducing mean stool volumes in people with cholera or in people with diarrhoea caused by Escherichia coli (low-quality evidence).

Chlorpromazine compared with placebo We don't know whether chlorpromazine is more effective at reducing the need of fluids or volume loss in people with severe watery diarrhoea (very low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review, but found 5 RCTs of three interventions versus placebo or no treatment. [67] [68] [69] [70] [71]

Racecadotril (acetorphan):
We found one RCT (110 people with acute diarrhoea associated with severe dehydration caused by *Vibrio cholerae)* comparing racecadotril (100 mg every 4 hours) versus placebo after initial rehydration. [67] The RCT found no significant difference in duration of diarrhoea between treatment groups (mean: 35 hours with racecadotril *v* 32 hours with placebo; OR –3, 95% CI –7.37 to +3.04; P = 0.13). The RCT also found no significant difference between mean total stool output or mean total oral rehydration solution (ORS) intake (mean stool output: 315 g/kg with racecadotril *v* 280 g/kg with placebo; OR –35, 95% CI –108.9 to +38.18; P = 0.34; mean total ORS intake: 309 mL/kg with racecadotril *v* 311 mL/kg with placebo; OR +2.00, 95% CI –57.45 to +60.37; P = 0.96). [67]

Berberine:
We found two RCTs comparing berberine versus placebo or no treatment. [68] [69] The first RCT (400 adults with acute watery diarrhoea) compared three interventions: berberine hydrochloride (100 mg tablet and 1 placebo capsule), tetracycline (500 mg capsule and 1 placebo tablet), berberine plus tetracycline (100 mg berberine tablet and 500 mg tetracycline capsule), or placebo (1 placebo tablet and 1 placebo capsule), given 4 times daily. [68] The RCT found similar results among groups in mean duration of diarrhoea among people with non-cholera diarrhoea (37 hours with berberine *v* 37 hours with placebo; 50 hours with tetracycline *v* 42 hours with placebo; 38 hours with berberine plus tetracycline *v* 42 hours with placebo; P values not reported). [68] However, among people with cholera, tetracycline and tetracycline plus berberine both significantly reduced mean duration of diarrhoea compared with placebo (35 hours with tetracycline *v* 65 hours with placebo; P <0.001; 41 hours with tetracycline plus berberine *v* 65 hours with placebo; P <0.001).

The second RCT (165 adults with acute diarrhoea caused by enterotoxigenic *Escherichia coli* [ETEC] and *Vibrio cholerae*) compared berberine sulphate versus no treatment. [69] People with ETEC diarrhoea received berberine sulphate (400 mg orally as a single dose) or no treatment. People with cholera received berberine sulphate (400 mg as a single dose) or berberine (1200 mg; 400 mg 8-hourly) plus tetracycline 1 g, tetracycline 1 g alone, or no treatment. The RCT did not report on overall duration of illness, but found that berberine sulphate significantly reduced mean stool volumes during three consecutive 8-hour periods after treatment in people who had ETEC diarrhoea compared with no treatment (P <0.05). The RCT also found that, in people with ETEC, berberine sulphate significantly increased the proportion of people who stopped having diarrhoea at 24 hours compared with no treatment (42% with berberine sulphate *v* 20% with no treatment; P <0.05; absolute numbers not reported). The RCT found that berberine sulphate significantly decreased mean stool volume at the second 8-hour period in people with cholera compared with no treatment (2.22 L with berberine sulphate *v* 2.79 L with no treatment; P <0.05). However, the RCT found that people with cholera who received berberine sulphate 1200 mg plus tetracycline did not have a significant reduction in stool output compared with people who received tetracycline alone (absolute numbers not reported). [69]

Chlorpromazine:
We found two RCTs comparing chlorpromazine versus placebo. [70] [71] The first RCT (410 people with severe watery diarrhoea aged under 2 years old, including 316 with cholera) compared a single dose of chlorpromazine 1 mg/kg versus placebo. [70] All participants were also given tetracycline (500 mg every 6 hours for 2 days) plus a single dose of chlorpromazine or placebo (1 mg/kg body weight) 2 hours after admission. The RCT found similar results between chlorpromazine and placebo in duration of hospital stay (children aged 2–8 years: 50 hours with chlorpromazine *v* 49 hours with placebo; adults: 43 hours with chlorpromazine *v* 44 hours with placebo; P values not reported), fluid requirements (children: 93.4 mL/kg with chlorpromazine *v* 104.3 mL/kg with placebo; adults: 100.2 mL/kg with chlorpromazine *v* 102.2 mL/kg with placebo; P values not reported) or volume loss (children: 250 mL/kg with chlorpromazine *v* 266 mL/kg with placebo; adults: 159 mL/kg with chlorpromazine *v* 189 mL/kg with placebo; P values not reported) in people with cholera. Results not reported for people in the non-cholera group. [70] The second RCT (46 adult males with severe dehydration caused by cholera) compared 4 doses of chlorpromazine (1 mg or 4 mg/kg as a single dose, given by mouth or injection) versus no treatment. [71] The RCT found that the duration of diarrhoea was significantly reduced among chlorpromazine-treated people compared with no treatment (92.1 hours with intramuscular [im] chlorpromazine 1 mg/kg *v* 99.0 hours with oral chlorpromazine 1 mg/kg *v* 94.6 hours with im chlorpromazine 4 mg/kg *v* 97.1 hours with oral chlorpromazine 4 mg/kg *v* 135.6 hours with no treatment; P values not reported). [71]

Harms: **Racecadotril:**
The RCT reported no drug-related adverse effects. [67]

Berberine:
The two RCTs gave no information on adverse effects. [68] [69]

Chlorpromazine:
The first RCT gave no information on adverse effects. [70] The second RCT reported a mild sedative effect for chlorpromazine. [71]

Comment: People received initial intravenous rehydration, standard WHO oral rehydration solution, to replace ongoing fluid losses, and doxycycline 300 mg [67] or tetracycline 500 mg every 6 hours for 2 days (dose reduced to 250 mg for children aged under 8 years). [70] In one study, [71] to be eligible, people were required to have continued losses of over 200 mL/hour for 16 hours after admission. Fluid replacement was given intravenously. No oral rehydration solutions or antibiotics were given in this study.

OPTION STANDARD ORAL REHYDRATION SOLUTION FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

We found no clinically important results from RCTs about oral rehydration compared with no rehydration in people with acute diarrhoea as RCTs assessing this intervention would be unethical. There is consensus that rehydration with standard oral rehydration solution is beneficial in people with severe diarrhoea.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: **Standard oral rehydration solutions versus no rehydration:**
We found no systematic review or RCTs. RCTs comparing oral rehydration versus no rehydration would be considered unethical.

Harms: **Standard oral rehydration solutions versus no rehydration:**
We found no RCTs.

Comment: **Clinical guide:**
Response to oral rehydration solutions in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION AMINO ACID REHYDRATION SOLUTIONS FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Symptom control
Amino acid oral rehydration solution compared with standard oral rehydration solution Amino acid oral rehydration solution may be more effective at reducing total volume of stool output in people with non-cholera diarrhoea, and at improving weight gain in people with cholera (very low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: **Amino acid oral rehydration solutions (ORS) versus standard ORS:**
We found two RCTs, which compared amino acid ORS versus standard ORS. [72] [73] The first RCT (97 men admitted to hospital with acute and severe dehydration from diarrhoea who received intravenous rehydration) found that amino acid ORS was associated with a non-significant reduction in the total duration of diarrhoea and significantly reduced the total volume of stool compared with standard ORS. [72] The second RCT (108 men with diarrhoea under 48 hours' duration and severe dehydration) found that amino acid ORS improved weight gain, but not stool volume, compared with standard ORS in people with cholera. [73] For people with non-cholera diarrhoea, amino acid ORS was associated with a reduction in stool volume, but not in weight gain. See table 5 for all results, p 36 .

Harms: **Amino acid oral rehydration solutions (ORS) versus standard ORS:**
The first RCT gave no information on harms. [72] The second RCT reported no episodes of hyper-natraemia or hyponatraemia in people taking amino acid ORS or standard ORS. [73]

Comment: **Clinical guide:**
Response to ORS in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION RICE-BASED ORAL REHYDRATION SOLUTION FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness

Rice-based oral rehydration solutions compared with glucose-based oral rehydration solutions Rice-based oral rehydration solutions may be more effective than glucose-based oral rehydration solutions at reducing the duration of diarrhoea in adults positive for Vibrio cholerae (low-quality evidence).

Rice-based oral rehydration solutions compared with low-glucose oral rehydration solution Rice-based oral rehydration solutions may be more effective than low-glucose oral rehydration solution at reducing the duration of diarrhoea in adults positive for Vibrio cholerae (low-quality evidence).

Low-sodium rice-based oral rehydration solution compared with rice-based oral rehydration solution Low-sodium rice-based oral rehydration solution may be more effective at reducing duration of diarrhoea in adults positive for Vibrio cholerae (low-quality evidence).

Other polymer-based oral rehydration solutions compared with glucose-based oral rehydration solutions Polymer-based oral rehydration solution (rice-based oral rehydration solution and amylase-resistant starch oral rehydration solution included in analysis) may be more effective than glucose-based oral rehydration solution at reducing the duration of diarrhoea in adults (low-quality evidence).

Symptom control

Rice-based oral rehydration solutions compared with glucose-based oral rehydration solutions Rice-based oral rehydration solutions may be more effective than glucose-based oral rehydration solutions at reducing total stool output in adults positive for Vibrio cholerae, but we don't know whether they are more effective at reducing vomiting or at reducing the unscheduled use of intravenous fluids (low-quality evidence).

Rice-based oral rehydration solutions compared with low-glucose oral rehydration solution Rice-based oral rehydration solutions may be more effective than low-glucose oral rehydration solution at reducing stool output in adults positive for Vibrio cholerae (low-quality evidence).

Low-sodium rice-based oral rehydration solution compared with rice-based oral rehydration solution Low-sodium rice-based oral rehydration solution may be more effective at reducing stool output in adults positive for Vibrio cholerae (low-quality evidence).

Other polymer-based oral rehydration solutions compared with glucose-based oral rehydration solutions We don't know whether high amylose maize starch oral rehydration solution is more effective than glucose-based oral rehydration solution at reducing the need for unscheduled intravenous fluids in adults with acute watery diarrhoea (low-quality evidence).

For GRADE evaluation of interventions for diarrhoea in adults (acute), **see table, p 37 .**

Benefits:

We found one systematic review (search date 2008), which included data on adults and children. [74] We have only reported data on adults here. The review included 6 RCTs that compared rice-based oral rehydration solution (ORS) versus glucose-based ORS. Of these, 4 RCTs were conducted only in adults, whereas two further RCTs included adults and children but presented separate data for adults. The 4 RCTs in adults and one of the two RCTs in adults and children only included people who were positive for *Vibrio cholerae*. The review reported that the original ORS was based on glucose and had an osmolarity of 310 mOsm/L (referred to as ORS 310 or greater in the review). A more recent formulation since 2004 had an osmolality of 245 mOsm/L (referred to as ORS 270 or less in the review). The review reported that all the trials in adults used an ORS of 310 or greater apart from one RCT that included an ORS 270 or less comparison. [74] This 4-armed RCT (123 male adults with severe cholera who had received initial rehydration with intravenous Ringer's lactate solution) compared rice-based ORS (50 g/L rice plus 90 mmol/L sodium); low-sodium rice-based ORS (50 g/L rice plus 70 mmol/L sodium); low-glucose and low-sodium ORS; and standard ORS (WHO ORS). [75] The review included one further small RCT (50 adults), which compared a high amylose maize starch ORS versus glucose ORS. [74]

Rice-based ORS versus glucose-based ORS:

The review pooled data for adults for duration of diarrhoea. It found that rice-based ORS significantly reduced the duration of diarrhoea compared with glucose-based ORS (4 RCTs, 228 adults; mean difference –7.11 hours, 95% CI –11.91 hours to –2.32 hours; P = 0.004). [74] Two RCTs included in the review reported on total stool output during the first 24 hours. Both RCTs found that rice-based ORS significantly improved total stool output compared with glucose-based ORS (first RCT: 89 adults, mean difference –143, 95% CI –207.1 to –78.9; second RCT: 157 adults, mean difference –43.7, 95% CI –47.3 to –40.1; units not reported). Two RCTs reported on vomiting. One RCT (50 adults) found no cases of vomiting with either group, while the second RCT found no significant

difference between groups in vomiting (89 adults; RR 0.96, 95% CI 0.7 to 1.3). Four RCTs reported on the unscheduled use of intravenous fluids. The review did not pool data for adults alone. One RCT (50 adults) found no cases with either group. The remaining three RCTs found no significant difference between groups (first RCT: 89 people; RR 0.89, 95% CI 0.56 to 1.41; second RCT: 113 people; RR 0.84, 95% CI 0.43 to 1.66; third RCT: 157 people; RR 0.01 to 3.48). [74] Of the 6 included RCTs, allocation concealment was unclear in 5 RCTs, 5 were unblinded, and all RCTs had adequate randomisation and inclusion of participants in the analysis.

Rice-based ORS versus low-glucose/low-sodium ORS:
The 4-arm RCT found that both rice-based ORS and low-sodium rice-based ORS significantly reduced stool output and duration of diarrhoea compared with low-glucose/low-sodium ORS (total stool output: 3.1 L with low-sodium rice-based ORS *v* 5.2 L with low-glucose/low-sodium ORS; 4.0 L with rice-based ORS *v* 5.2 L with standard ORS; P <0.05; duration of diarrhoea: 36.5 hours with rice-based ORS *v* 28.9 hours with low-sodium rice-based ORS *v* 46.9 hours with standard ORS; P <0.05 for comparisons *v* standard ORS). [75] See table 5, p 36 .

Low-sodium rice-based ORS versus rice-based ORS:
The 4-arm RCT found that low-sodium rice-based ORS containing sodium 70 mmol/L significantly reduced stool output and duration of diarrhoea compared with rice-based ORS containing 90 mmol/L sodium (total stool output: 3.1 L with low-sodium rice-based ORS *v* 4.0 L with rice-based ORS; P <0.05). [75] See table 5, p 36 .

Other polymer-based ORS versus glucose-based ORS:
The review included any polymer-based oral rehydration solution and included one RCT (50 males aged 18–65 years, acute watery diarrhoea; bloody diarrhoea excluded), which compared a high amylose maize starch ORS versus glucose ORS. [74] The review found no significant difference between groups in the unscheduled use of intravenous fluids (9/25 [36%] with high amylose maize starch ORS *v* 12/25 [48%] with glucose ORS; RR 0.75, 95% CI 0.39 to 1.46). One further small RCT included an amylase-resistant starch ORS arm (16 adults) as well as a rice ORS arm (16 people) and glucose ORS arm (16 people). The RCT found that polymer-based ORS (rice and amylase-resistant starch) significantly reduced the duration of diarrhoea compared with glucose ORS (mean duration: 63.75 hours with polymer-based [rice and amylase-resistant starch] *v* 90.9 hours with glucose ORS; difference –27.15 hours, 95% CI –43.24 hours to –11.06 hours). [74]

Harms:

Rice-based oral rehydration solution (ORS) versus glucose-based ORS:
One included RCT found no significant difference between groups in the occurrence of hyponatraemia (57 adults; RR 0.89, 95% CI 0.27 to 2.97). [74]

Rice-based ORS versus low-glucose/low-sodium ORS:
The RCT gave no information about harms. [75]

Low-sodium rice-based ORS versus rice-based ORS:
The RCT gave no information about harms. [75]

Other polymer-based ORS versus glucose-based ORS:
The RCT comparing a high amylose maize starch ORS versus glucose ORS found no significant difference between groups in hyponatraemia (50 adults; RR 1.50, 95% CI 0.27 to 8.22). [74]

Comment:

Clinical guide:
Rice-based oral rehydration solution (ORS) is associated with a significant reduction in duration of diarrhoea when compared with any glucose-based ORS.

Response to ORS in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION BICARBONATE ORAL REHYDRATION SOLUTION FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness
Bicarbonate oral rehydration solution compared with standard oral rehydration solution We don't know whether bicarbonate oral rehydration solution is more effective at reducing the duration of diarrhoea in people with cholera and non-cholera diarrhoea (very low-quality evidence).

Bicarbonate oral rehydration solution compared with chloride oral rehydration solution We don't know whether bicarbonate oral rehydration solution is more effective at reducing the duration of diarrhoea in people with cholera and severe dehydration (low-quality evidence).

Symptom control

Bicarbonate oral rehydration solution compared with standard oral rehydration solution We don't know whether bicarbonate oral rehydration solution is more effective at reducing the volume of diarrhoea in people with cholera and non-cholera diarrhoea (very low-quality evidence).

Bicarbonate oral rehydration solution compared with chloride oral rehydration solution We don't know whether bicarbonate oral rehydration solution is more effective at reducing total stool output in people with cholera and severe dehydration (low-quality evidence).

Benefits:

Bicarbonate oral rehydration solution (ORS) versus standard ORS:
We found no systematic review but found two RCTs. [76] [77] The first RCT (180 men with diarrhoea lasting <48 hours) found no significant difference between treatments in the duration or volume of diarrhoea. [76] The second RCT (130 people with cholera) did not assess the significance of the difference between groups, although bicarbonate ORS increased duration and volume of diarrhoea compared with standard ORS (see table 5, p 36). [77]

Bicarbonate ORS versus chloride ORS:
We found no systematic review but found one small RCT (60 people with cholera and severe dehydration) comparing bicarbonate ORS versus an otherwise identical ORS, in which the bicarbonate was replaced with chloride. [78] The RCT found no significant difference between treatments in total stool output or duration of diarrhoea (see table 5, p 36).

Harms:

Bicarbonate oral rehydration solution (ORS) versus standard ORS:
The first RCT gave no information on harms. [76] The second RCT (130 people with cholera) reported that significantly more people taking standard ORS thought that it tasted "bad" than did those taking bicarbonate ORS (29% with standard ORS *v* 13% with bicarbonate ORS; P value not reported). [77]

Bicarbonate ORS versus chloride ORS:
The RCT gave no information on harms. [78]

Comment:

All people with cholera received antibiotic treatment in addition to fluid treatment. Oral tetracycline or doxycycline were widely used, and were initiated at varying intervals after the start of oral rehydration.

Clinical guide:
Response to ORS in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION REDUCED OSMOLARITY ORAL REHYDRATION SOLUTION FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness

Low-glucose oral rehydration solution compared with rice-based oral rehydration solution Low-glucose oral rehydration solution may be less effective at reducing the duration of diarrhoea in adults positive for Vibrio cholerae (low-quality evidence).

Low-sodium rice-based oral rehydration solution compared with rice-based oral rehydration solution Low-sodium rice-based oral rehydration solution may be more effective at reducing the duration of diarrhoea in adults positive for Vibrio cholerae (low-quality evidence).

Symptom control

Low-glucose oral rehydration solution compared with rice-based oral rehydration solution Low-glucose oral rehydration solution may be less effective at reducing stool output in adults positive for Vibrio cholerae (low-quality evidence).

Low-sodium rice-based oral rehydration solution compared with rice-based oral rehydration solution Low-sodium rice-based oral rehydration solution may be more effective at reducing stool output in adults positive for Vibrio cholerae (low-quality evidence).

Note

Reduced osmolarity oral rehydration solution has been associated with an increased risk of non-symptomatic hyponatraemia.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

Reduced osmolarity oral rehydration solution (ORS) versus standard ORS:
We found 4 RCTs, which compared reduced osmolarity ORS versus standard ORS, all of which evaluated people with cholera. The RCTs found a small and inconsistent effect on total volume of stool and duration of diarrhoea with reduced osmolarity ORS compared with standard ORS (see table 5), p 36 . [79] [80] [75] [81]

Reduced osmolarity ORS versus rice-based ORS:
See benefits of Rice-based oral rehydration solution: severe diarrhoea in resource-poor countries, p 23 .

Harms:

Reduced osmolarity oral rehydration solution (ORS) versus standard ORS:
The first RCT found that reduced osmolarity ORS significantly increased asymptomatic hyponatraemia compared with standard ORS (OR 2.1, 95% CI 1.1 to 4.1). [79] The second RCT found that more people developed non-symptomatic hyponatraemia with reduced osmolarity ORS than with standard ORS, but that the difference was not significant (3/34 [9%] with reduced osmolarity ORS *v* 0/29 [0%] with standard ORS; P = 0.264). [80] The third RCT gave no information on harms. [75] The fourth RCT found no significant difference in asymptomatic hyponatraemia between groups (RR 1.1, 95% CI 0.5 to 2.7), and reported that no one developed hyponatraemia with symptoms. [81]

Reduced osmolarity ORS versus rice-based ORS:
See harms of Rice-based oral rehydration solution: severe diarrhoea in resource-poor countries, p 23 .

Comment:

Clinical guide:
Response to oral rehydration solution in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION INTRAVENOUS REHYDRATION FOR SEVERE DIARRHOEA IN RESOURCE-POOR COUNTRIES

Duration of illness
Intravenous rehydration compared with enteral rehydration We don't know whether intravenous rehydration is more effective at reducing duration of diarrhoea in people with cholera and severe dehydration (low-quality evidence).

Symptom control
Intravenous rehydration compared with enteral rehydration We don't know whether intravenous rehydration is more effective at reducing total volume of stool passed in people with cholera and severe dehydration (low-quality evidence).

Note
We found no clinically important results about oral rehydration solution alone compared with intravenous rehydration in people with acute diarrhoea.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits:

Intravenous rehydration versus oral rehydration solution (ORS):
We found no systematic review or RCTs comparing ORS alone versus intravenous rehydration.

Intravenous rehydration versus enteral rehydration:
We found one small RCT (20 adults with cholera and severe dehydration, who had received initial intravenous fluids for up to 90 minutes) comparing intravenous rehydration versus enteral rehydration through a nasogastric tube. [82] All people with cholera received antibiotic treatment in addition to fluid treatment. Oral tetracycline or doxycycline were widely used, and were initiated at varying intervals after the start of oral rehydration. The RCT found no significant difference in the total duration of diarrhoea, total volume of stool passed, or duration of *Vibrio* excretion (duration of diarrhoea: 44 hours with intravenous [iv] fluids *v* 37 hours with nasogastric fluids; difference +7 hours, 95% CI –6 hours to +20 hours; total volume of stool passed: 8.2 L with iv fluids *v* 11 L with nasogastric fluids; difference –2.9 L; duration of *Vibrio* excretion: 1.1 days with iv fluids *v* 1.4 days with nasogastric fluids; difference 0.3 days, 95% CI 0 days to 1 day). See table 5, p 36 .

Harms:

Intravenous rehydration versus oral rehydration solution:
We found no RCTs.

Intravenous rehydration versus enteral rehydration:
The RCT reported that there was no unusual morbidity in either treatment group (no further data reported). [82]

Comment: **Clinical guide:**
Response to oral rehydration solution in people with cholera may not be comparable with response in people with less severe forms of diarrhoea.

OPTION ZINC SUPPLEMENTATION FOR DIARRHOEA IN RESOURCE-POOR COUNTRIES New

We found no direct information from RCTs about the use of zinc supplementation in treating severe diarrhoea in adults living in resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs that assessed zinc supplementation in acute diarrhoea in adults.

Harms: We found no RCTs.

Comment: **Clinical guide**
Although the World Health Organization recommends routine zinc supplementation in children with diarrhoea in low-resource settings, [83] we found no RCT evidence for or against the use of zinc supplementation in adult diarrhoea.

OPTION VITAMIN A SUPPLEMENTATION IN ACUTE DIARRHOEA IN RESOURCE-POOR COUNTRIES New

We found no direct information from RCTs about the use of vitamin A supplementation in treating severe diarrhoea in adults living in resource-poor countries.

For GRADE evaluation of interventions for diarrhoea in adults (acute), see table, p 37 .

Benefits: We found no systematic review or RCTs that assessed vitamin A supplementation in acute diarrhoea in adults.

Harms: We found no RCTs.

Comment: **Clinical guide**
We found no RCT evidence for or against the use of vitamin A supplementation in adult diarrhoea.

GLOSSARY

Acute diarrhoea An episode of diarrhoea lasting 14 days or less.

Severe diarrhoea A diarrhoeal illness associated with profuse or dehydrating stool losses, blood, fever, or illness in infants, elderly people, or immunocompromised people.

Travellers' diarrhoea Diarrhoea occurring during or shortly after travel in people who have crossed a national boundary.

Empirical treatment Treatment guided by professional experience, or given before or without reference to the results of microbiological investigations.

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Very low-quality evidence Any estimate of effect is very uncertain.

SUBSTANTIVE CHANGES

Zinc supplementation for diarrhoea in resource-poor countries New option added. Categorised as Unknown effectiveness as we found no RCT evidence to assess its effects.

Vitamin A supplementation in acute diarrhoea in resource-poor countries New option added. Categorised as Unknown effectiveness as we found no RCT evidence to assess its effects.

Oral rehydration solutions for mild-to-moderate diarrhoea in resource-poor countries New evidence added. [65] Categorisation unchanged (Unknown effectiveness) as there remains insufficient evidence to judge the effects of this intervention.

Rice-based oral rehydration solution for severe diarrhoea in resource-poor countries New evidence added. [74] Categorisation unchanged (Beneficial).

Antibiotics plus antimotility agents for travellers' diarrhoea New evidence added. [50] Categorisation changed from Unknown effectiveness to Likely to be beneficial.

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Disclaimer

TABLE 1 **Percentage of individuals with diarrhoea (cases) or controls with given aetiological agent found on stool testing**

Population	GP attendants in the Netherlands [8]	European and North American travellers in Kenya, India*, or Jamaica with diarrhoea [7]		
Age	15–29 years	30–59 years	60 years or over	Age range not stated
Number	(170 cases/72 controls)	(313 cases/244 controls)	(102 cases/102 controls)	(1079 cases)
Percentage (%) positive for:				
Adenovirus	1.0/0.0	0.6/1.4	0.3/0.0	2.8
Aeromonas species	–	–	–	1.9
Astrovirus	0.6/0.0	0.6/0.0	3.9/2.0	–
Blastocystis hominis	27.2/34.7	23.9/34.4	16.7/37.3	–
Campylobacter species	14.7/0.0	10.5/1.2	7.8/0.0	4.2
Cryptosporidium species	3.0/0.0	0.6/0.0	0.0/0.0	0.6
Cyclospora species	0.6/0.0	0.3/0.0	0.0/0.1	–
Dientamoeba fragilis	8.3/18.1	8.9/17.4	9.8/13.7	–
Entamoeba histolytica/ dispar	0.0/2.8	1.0/0.8	1.0/0.0	1.5
Enterotoxigenic *Escherichia coli*	–	–	–	25.5
Giardia lablia	3.0/0.0	5.7/1.2	3.9/3.9	0.7
Norwalk-like virus	5.9/1.4	3.9/0.8	1.0/1.0	–
Plesiomonas species	–	–	–	6.3
Rotavirus	4.1/1.4	1.9/1.6	2.9/0.0	2.6
Salmonella species	3.5/0.0	2.6/0.0	3.9/1.0	6.3
Sapporo-like virus	2.9/0.0	0.6/0.7	0.0/0.0	–
Shigella species	0.0/0.0	0.0/0.0	0.0/0.0	6.6
Vibrio species	–	–	–	3.1
Verocytoxin-producing *Escherichia coli*	0.0/1.6	0.7/0.4	0.0/1.1	–
Yersinia species	1.2/0.0	0.3/1.6	2.0/2.0	–

*In India, stool samples were not obtained from May to September because of lack of tourism.

TABLE 2 **Antibiotics (empirical use for mild-to-moderate diarrhoea)**

Ref	Comparison	Participants	Results	Adverse effects
[22]	Nifuroxazide (400 g bd for 5 days) *v* placebo	102 adults in France with acute diarrhoea (<3 watery stools a day)	**Duration of diarrhoea** Significant reduction in mean duration of diarrhoea with nifuroxazide (2.09 days with nifuroxazide *v* 3.26 days with placebo; P <0.004) **Symptom control** Significant reduction in number of bowel movements a day on days 1 and 2, did not reach significance on day 3: (day 1: 3.09 with nifuroxazide *v* 4.40 with placebo; P <0.015; day 2: 1.89 with nifuroxazide *v* 2.79 with placebo; P <0.008; day 3: 1.46 with nifuroxazide *v* 1.98 with placebo; NS) **Microbiological efficacy** Not reported.	The RCT found no adverse effects
[23]	Ciprofloxacin (500 mg bd for 5 days) *v* TMP-SMX (160 mg/800 mg bd for 5 days) *v* placebo	202 adults in the US with acute diarrhoea defined as >3 unformed stools in the previous 24 hours or >2 unformed stools in the 8 hours before presentation	**Duration of diarrhoea** Ciprofloxacin significantly shortened the duration of diarrhoea compared with placebo (2.4 days with ciprofloxacin *v* 3.4 days with placebo; P <0.0005). Similar duration of diarrhoea with TMP-SMX and placebo in people identified as having a bacterial pathogen (days to last unformed stool: 4.2 days with TMP-SMX *v* 4.0 days with placebo; significance not reported) **Symptom control** Ciprofloxacin significantly increased the proportion of people cured or improved by days 1, 3, 4, and 5 compared with placebo (P <0.05). TMP-SMX increased the proportion of people cured or improved compared with placebo, only the difference on day 3 was significant (proportion of people cured or improved on day 3: 76% with TMP-SMX *v* 58% with placebo; P <0.05) **Microbiological efficacy** 61 pathogens (mainly *Campylobacter*, *Shigella*, and *Salmonella*) were isolated from 57/202 (28%) people. The RCT found that ciprofloxacin was significantly more effective in eradication of pathogens than placebo (number of negative stool samples: 14/17 [82%] with ciprofloxacin *v* 4/19 [21%] with placebo; P <0.001), or TMP-SMX (number of negative stool samples: 14/17 [82%] with ciprofloxacin *v* 12/25 [48%] with TMP-SMX; P <0.001)	20 adverse effects with ciprofloxacin (4 people with headache, 4 with myalgia, 3 with sleep disturbances, 3 with nausea, 2 with rash, 1 each with vaginitis, dysphagia, dizziness, and bitter taste) 23 with TMP-SMX (8 people with headache, 4 with rash, 3 with dizziness, 3 with nausea, 2 with sleep disturbances, 1 each with dysuria, bloating, and a sour taste) 12 with placebo (5 people with headache, 2 with nausea, 2 with dizziness, 1 each with myalgias, dysuria, and rash) Complaints were self-limiting; however, treatment was discontinued in people with rash Bacterial resistance to ciprofloxacin developed in 2/10 (20%) people and to TMP-SMX in 3/14 (21%) people with *Campylobacter* isolates
[24]	Single-dose ofloxacin 400 mg *v* placebo	117 adults in Spain with acute gastroenteritis, defined as >2 unformed stools in the previous 24 hours or >2 in the previous 8 hours with fever, abdominal pain, urgency, or other gastrointestinal complaints	**Duration of diarrhoea or fever** No significant difference between ofloxacin and placebo in the average duration of diarrhoea (2.51 days with ofloxacin *v* 3.41 days with placebo; P = 0.117), but found that ofloxacin significantly reduced duration of fever compared with placebo (0.63 days with ofloxacin *v* 1.05 days with placebo; P = 0.02) **Symptom control** No significant difference in the proportion of people with unchanged symptoms for more than 48 hours between ofloxacin and placebo (3/44 [7%] with ofloxacin *v* 6/46 [13%] with placebo; P = 0.485) **Microbiological efficacy** Pathogens (mainly *Salmonella enteritidis*) were isolated from 72/117 (62%) participants. Ofloxacin was significantly more effective in eradication of pathogens after 2 days of treatment compared with placebo (number of people with negative stool samples after 2 days: 36/53 (68%) with ofloxacin *v* 23/56 (41%) with placebo; P = 0.0018). The RCT found no significance difference in eradication of pathogens on day 15 with ofloxacin compared with placebo (number of people with negative stool samples on day 15: 33/43 [77%] with ofloxacin *v* 32/45 [71%] with placebo; P = 0.63)	The RCT found no difference in adverse effects between treatment groups (1 person with headache with ofloxacin and 1 person with rash with placebo; no treatment required; P value not reported)

Ref	Comparison	Participants	Results	Adverse effects
[25]	Ciprofloxacin (500 mg bd for 5 days) *v* placebo	173 adults in the UK with severe acute gastroenteritis, defined as >4 fluid stools in 24 hours with at least 1 of the following symptoms: abdominal pain, fever, vomiting, myalgia, or headache	**Duration of diarrhoea** Ciprofloxacin significantly reduced duration of diarrhoea (2.2 days with ciprofloxacin *v* 4.6 days with placebo; P <0.0001) and other gastrointestinal symptoms after treatment compared with placebo (1.9 days with ciprofloxacin *v* 4.3 days with placebo; P <0.0001) **Symptom control** Ciprofloxacin significantly reduced the proportion of people with unresolved symptoms compared with placebo (3/81 [4%] with ciprofloxacin *v* 17/81 [21%] with placebo; P <0.001) **Microbiological efficacy** Pathogens (mainly *Campylobacter* and *Salmonella* species) were isolated from 141/162 (87%) of participants. Ciprofloxacin increased the proportion of people with negative stool samples on day 5 compared with placebo (59/69 [86%] people with ciprofloxacin *v* 23/67 [34%] with placebo; P value not reported). It found no significant difference in eradication of pathogens 6 weeks after treatment between the 2 groups (8/67 [12%] with ciprofloxacin *v* 8/65 [12%] with placebo; P value not reported)	The RCT found 2 adverse effects with ciprofloxacin that could be attributed to the treatment (1 each with unpleasant taste and vaginal thrush); the number of adverse effects in the placebo group was not reported. No bacterial resistance developed during treatment
[26]	Compared 5- and 7-day regimens of pefloxacin 400 mg once daily *v* symptomatic treatment (described as standard supportive regimen)	82 adults in Croatia with acute bacterial gastroenterocolitis, defined as >3 loose stools in 24 hours, fever >38 °C, and at least 1 of abdominal pain, nausea, or vomiting	**Duration of fever** Both empirical pefloxacin regimens reduced the mean duration of fever days compared with symptomatic treatment (3.3 days with 5-day pefloxacin *v* 5.0 days with symptomatic treatment; P <0.001; 3.0 days with 7-day pefloxacin *v* 5.0 days with symptomatic treatment; P <0.001). The RCT found no significant difference in the mean duration of fever days between the two pefloxacin regimens (P = 0.261) **Symptom control** Both pefloxacin regimens significantly reduced the average number of loose stools a day compared with symptomatic treatment (day 3: 3.0 with 5-day pefloxacin *v* 4.2 with symptomatic treatment, 3.0 with 7-day pefloxacin *v* 4.2 with symptomatic treatment; day 5: 1.5 with 5-day pefloxacin *v* 4.0 with symptomatic treatment, 1.6 with 7-day pefloxacin *v* 4.0 with symptomatic treatment; day 7: 1.2 with 5-day pefloxacin *v* 2.1 with symptomatic treatment, 1.4 with 7-day pefloxacin *v* 2.1 with symptomatic treatment; P <0.001). It found no significant difference in the average number of loose stools a day between the two pefloxacin regimens (P >0.23) **Microbiological efficacy** Pathogens (mainly *S enteritidis* and *Salmonella typhimurium*) were isolated from all 82 (100%) participants. The RCT found that both pefloxacin regimens were significantly more effective in eradication of pathogens from day 5 onwards compared with symptomatic treatment (number of people with negative stool samples on day 5: 18/20 [90%] with 5-day pefloxacin *v* 21/35 [60%] with symptomatic treatment; P = 0.049; 23/27 [93%] with 7-day pefloxacin *v* 21/35 [60%] with symptomatic treatment; P = 0.017; day 7: 19/20 [95%] with 5-day pefloxacin *v* 22/35 [63%] with symptomatic treatment; 23/27 [93%] with 7-day pefloxacin *v* 22/35 [63%] with symptomatic treatment; P values reported as significant; CI not reported). Both pefloxacin regimens achieved eradication of pathogens in all 47 (100%) people 1 week after treatment compared with 29/35 (87%) people with symptomatic treatment (P value not reported). All participants had negative stool samples 4 weeks after treatment	The RCT found no adverse effects requiring discontinuation of treatment with pefloxacin

bd, twice a day; NS, not significant; TMP-SMX, trimethoprim–sulfamethoxazole (co-trimoxazole).

TABLE 3 **Effects of antibiotics for travellers' diarrhoea**

Ref	Antibiotics	Participants	Duration of illness after start of treatment	Adverse effects
Ciprofloxacin				
[34]	Ciprofloxacin 250 mg bd for 3 days *v* placebo	17 travellers from Houston, Texas to Mexico with 4 or more loose stools or 2 or more loose stools plus any of: 38.0 °C or more oral temperature, vomiting, or abdominal cramps during previous 24 hour period	Mean time to cure: 26 hours with ciprofloxacin *v* 60 hours with placebo; P = 0.03	No adverse effects reported
[35]	Ciprofloxacin 500 mg (single dose) *v* placebo	83 British troops having 1 or more loose stools in Belize	Mean time to last liquid stool: 20.9 hours with ciprofloxacin *v* 50.4 hours with placebo; P <0.0001; mean time to last unformed stool: 24.8 hours with ciprofloxacin *v* 53.5 hours with placebo; P <0.0001)	No adverse effects reported
Ofloxacin				
[43]	Ofloxacin 300 mg bd for 5 days *v* 3 days *v* placebo	232 adults (66 with ofloxacin for 5 days *v* 81 with ofloxacin for 3 days *v* 79 with placebo) (acute diarrhoea 4 or more unformed stools in 24 hours or 3 or more unformed stools in 8 hours, plus fever or other gastrointestinal complaint)	Mean: 39 hours with ofloxacin for 5 days (P = NS compared with placebo) *v* 28 hours with ofloxacin for 3 days (P <0.05 compared with placebo) *v* 56 hours with placebo	3/68 (4%) with ofloxacin for 5 days *v* 4/84 (5%) with ofloxacin for 3 days (insomnia, dizziness, dysgeusia [2 each], sleep disorder, nausea, vaginitis [1 each]). Two people with ofloxacin discontinued (nausea and vaginitis, and headache and rash)
[84]	Ofloxacin 400 mg single dose *v* ofloxacin 200 mg bd for 3 days *v* ofloxacin 400 mg single dose plus loperamide (4 mg then 2 mg after each loose stool)	166 adults (56 with ofloxacin single dose *v* 56 with ofloxacin bd *v* 54 with ofloxacin plus loperamide) (3 or more unformed stools in 24 hours plus 1 additional symptom of enteric disease)	Median: 14 hours with ofloxacin single dose *v* 28 hours with ofloxacin bd *v* 0 hours with ofloxacin plus loperamide (P <0.001)	No clinically important adverse reactions reported
Aztreonam				
[42]	Aztreonam 100 mg 3 times/day for 5 days *v* placebo	191 adults (98 with aztreonam *v* 93 with placebo) (acute diarrhoea 4 or more unformed stools in 24 hours or 3 in 8 hours, plus 1 or more additional symptoms of abdominal pain or cramps, nausea, vomiting, or fever)	Median: 33 hours with aztreonam *v* 68 hours with placebo (P = 0.0001)	18/98 (18%) with aztreonam *v* 12/93 (13%) with placebo experienced adverse effects (mild gastrointestinal complaints: 4 with aztreonam *v* 2 with placebo; respiratory symptoms: 9 with aztreonam *v* 8 with placebo) (NS; P value not reported)
Trimethoprim–sulfamethoxazole (co-trimoxazole)				
[28]	TMP-SMX (320 mg/1600 mg) single dose *v* TMP-SMX (160 mg/800 mg) bd for 3 days *v* loperamide hydrochloride (4 mg initially, 2 mg after each loose stool, 16 mg/day or more) *v* TMP-SMX (160 mg/800 mg) bd for 3 days plus loperamide hydrochloride (4 mg initially, 2 mg after each loose stool, 16 mg/day or more) *v* placebo	227 adults (44 with TMP-SMX single dose *v* 45 with TMP-SMX for 3 days *v* 46 with loperamide *v* 47 with TMP-SMX bd plus loperamide *v* 45 with placebo) (3 or more unformed stools in 24 hours plus 1 additional symptom of enteric disease)	Mean: 28 hours with TMP-SMX single dose *v* 36 hours with TMP-SMX for 3 days *v* 33 hours with loperamide *v* 16 hours with TMP-SMX bd plus loperamide *v* 58 hours with placebo (P less-than or equal to 0.005 compared with active treatments)	1 person taking TMP-SMX for 3 days had a self-limiting rash
[39]	BW942C (20 mg initially then 10 mg 5 times/day) *v* TMP-SMX (160 mg/800 mg bd) *v* BW942C (20 mg initially then 10 mg 5 times/day) plus TMP-SMX (160 mg/800 mg bd) *v* placebo; for 72 hours	134 adults (31 with BW942C *v* 31 with TMP-SMX *v* 31 with BW942C plus TMP-SMX *v* 33 with placebo) (acute diarrhoea 4 or more unformed stools in 24 hours or 3 in 8 hours, plus 1 additional symptom of enteric disease)	24 hours with TMP-SMX *v* 59 hours with placebo (P = 0.001)	9/32 (28%) with BW942C *v* 2/31 (6%) with TMP-SMX *v* 3/33 (9%) with BW942C plus TMP-SMX *v* 1/33 (3%) with placebo (dizziness, light-headedness, restlessness, sleeplessness, difficulty concentrating, confusion or euphoria within the first 24 hours)

Ref	Antibiotics	Participants	Duration of illness after start of treatment	Adverse effects
[40]	Ciprofloxacin 500 mg *v* TMP-SMX (160 mg/800 mg) *v* placebo bd for 5 days	181 adults (60 with ciprofloxacin *v* 59 with TMP-SMX *v* 62 with placebo) (acute diarrhoea 4 or more unformed stools in 24 hours or 3 in 8 hours plus 1 or more symptom of enteric disease)	Mean: 29 hours with ciprofloxacin *v* 20 hours with TMP-SMX *v* 81 hours with placebo (P less-than or equal to 0.001 compared with active treatment)	2 with ciprofloxacin (pruritus of the hands and eyes/swelling of hand and lips; vaginal infection) *v* 1 with TMP-SMX (halos around lights)
[41]	TMP-SMX (160 mg/800 mg bd for 3 days) plus loperamide (4 mg then 2 mg after each loose stool, 16 mg/day or less, for 3 days) *v* TMP-SMX (320 mg/1600 mg single dose) plus loperamide (4 mg then 2 mg after each loose stool, 16 mg/day or less, for 3 days) *v* TMP-SMX (320/1600 mg loading dose then 160 mg/800 mg bd for 5 doses) plus loperamide (4 mg then 2 mg after each loose stool, 16 mg/day or less, for 3 days)	190 adults (62 with TMP-SMX bd plus loperamide *v* 64 with TMP-SMX single dose plus loperamide *v* 64 with TMP-SMX loading dose plus loperamide) (6 or more unformed stools in 24 hours)	Time until 50% well: 11 hours with TMP-SMX bd plus loperamide *v* 4 hours with TMP-SMX single dose plus loperamide *v* 0 hours with TMP-SMX loading dose plus loperamide (P <0.09 favouring TMP-SMX loading dose plus loperamide); time until 75% well: 34 hours with TMP-SMX bd plus loperamide *v* 33 hours with TMP-SMX single dose plus loperamide *v* 12 hours with TMP-SMX loading dose plus loperamide (P <0.09 favouring TMP-SMX loading dose plus loperamide)	No adverse effects reported
[36]	TMP-SMX (160 mg/800 mg bd for 5 days) *v* TMP (200 mg bd for 5 days) *v* placebo	110 adults (37 with TMP-SMX *v* 38 with TMP *v* 35 with placebo) (diarrhoea 4 or more unformed stools in 24 hours or 3 or more in 8 hours, plus 1 or more additional symptom of enteric disease)	29.2 hours with TMP-SMX *v* 30.7 hours with TMP *v* 92.8 hours with placebo (P <0.0001)	1 (3%) person with TMP had minimal self-limiting rash
Bicozamycin				
[37]	Bicozamycin (500 mg 4 times/day for 3 days) *v* placebo	140 adults (72 with bicozamycin *v* 68 with placebo) (acute diarrhoea 4 or more unformed stools in 24 hours plus 1 additional symptom of enteric disease)	28.2 hours with bicozamycin *v* 63.7 hours with placebo (P = 0.00009)	Minor rash in 4/78 (5%) people with bicozamycin *v* 1/68 (1%) person with placebo (significance of difference between groups not reported). 1 person taking bicozamycin had an eruption (erythematous macular patches)
Furazolidone *v* ampicillin				
[38]	Furazolidone (100 mg 4 times/day for 5 days) *v* ampicillin (500 mg 4 times/day for 5 days)	94 adults (47 in each group) (4 or more unformed stools in 24 hours or 3 unformed stools in 8 hours)	Mean: 57 hours with furazolidone *v* 72 hours with ampicillin (NS; P value not reported)	9/17 (53%) with furazolidone *v* 2/20 (10%) with ampicillin who had consumed alcohol had facial flushing. 12/47 (26%) with furazolidone had dark-yellow urine.

bd, twice a day; NS, not significant; TMP, trimethoprim; TMP–SMX, trimethoprim–sulfamethoxazole (co-trimoxazole).

TABLE 4 **Effects of antibiotics plus antimotility agents for travellers' diarrhoea**

Reference and population	Intervention	Comparison	Outcome	Results	P value
Antibiotics plus antimotility agents *v* antimotility agents alone					
[28] RCT (227 US students travelling in Mexico)	TMP-SMX (160 mg/800 mg twice daily for 3 days) plus loperamide (4 mg as a loading dose plus 2 mg after each loose stool)	Loperamide alone (4 mg as a loading dose plus 2 mg after each loose stool)	Mean duration of diarrhoea (time to last unformed stool)	16 hours with TMP-SMX plus loperamide *v* 33 hours with loperamide alone	P <0.005
Different antibiotics plus antimotility agents regimens *v* each other					
[51] RCT (142 US soldiers deployed in Thailand who developed diarrhoea)	Ciprofloxacin 750 mg single dose plus loperamide (4 mg as a loading dose plus 2 mg after each loose stool)	Ciprofloxacin (500 mg twice daily for 3 days) plus loperamide (4 mg as a loading dose plus 2 mg after each loose stool)	Proportion of people fully recovered at 24 hours	36% with single-dose ciprofloxacin plus loperamide *v* 38% with 3-day ciprofloxacin plus loperamide	P value not reported; reported as not significant
			Proportion of people fully recovered at 48 hours	70% with single-dose ciprofloxacin plus loperamide *v* 64% with 3-day ciprofloxacin plus loperamide	P value not reported; reported as not significant
			Proportion of people fully recovered at 72 hours	83% with single-dose ciprofloxacin plus loperamide *v* 82% with 3-day ciprofloxacin plus loperamide	P value not reported; reported as not significant
			Mean time to last unformed stool	34 hours with single-dose ciprofloxacin plus loperamide *v* 44 hours with 3 day ciprofloxacin plus loperamide	P value not reported
			Mean time to relief of all symptoms	40 hours with single-dose ciprofloxacin plus loperamide *v* 45 hours with 3-day ciprofloxacin plus loperamide	P value not reported

NS, reported as not significant; TMP-SMX, trimethoprim–sulfamethoxazole (co-trimoxazole).

TABLE 5 **Effects of oral rehydration solutions (ORS) in severe diarrhoea in adults living in resource-poor countries.**

Trial	People	Aetiology	Total duration of diarrhoea (hours)			Total volume of stool		
			Control	Intervention	Difference (95% CI)	Control	Intervention	Difference (95% CI)
Intravenous fluid *v* ORS after initial intravenous fluids								
[82]	20 men over 20 years of age	Cholera (100%)	44	37	7 (–6 to +20)	8.2 L	11.1 L	–2.9 L (NA)
Amino acid ORS *v* standard ORS								
[72]	97 males aged 6–59 years	Cholera (60%)	52	44	8 (–1 to +14)	393 mL/kg	236 mL/kg	157 mL/kg (97 mL/kg to 298 mL/kg) P = 0.0003
[73]	108 adult men, mean age 33 years	Cholera (79%)	NA	NA	NA	Presented graphically	Presented graphically	Presented graphically
Bicarbonate ORS *v* standard ORS								
[76]	180 people aged 8–56 years	Cholera, ETEC	48	48	0 (–0.5 to +8) P = 0.32	390 mL/kg	366 mL/kg	24 mL/kg (–18 mL/kg to 118 mL/kg) P = 0.10
[77]	130 people	Cholera	36	30	6 (NA)	6025 mL	4252 mL	1753 mL (NA)*
Bicarbonate ORS *v* chloride ORS								
[78]	60 adults	Cholera	33	33	0 (NA) P = 0.98	4.1 mL/kg/hour	4.5 mL/kg/hour	0.4 mL/kg/hour (NA) P = 0.53
Reduced osmolarity ORS *v* standard ORS								
[79]	300 people	Cholera	43	46	3 (0.8 to 7)	273 g/kg	284 g/kg	+11 g/kg (–25 g/kg to +47 g/kg)
[75]	63 adult men	Cholera	47	37	10 (4.2 to 15.2)	5.2 L	4.5 L	+0.7 L (–0.04 L to +1.4 L)
[80]	34 adults	Cholera	57	50	7 (NA) P = 0.126	481 mL/kg	303 mL/kg	178 mL/kg (NA) P = 0.001
[81]	176 adults	Cholera	43	44	Difference between groups reported as non-significant; P value not reported	3894 mL/kg	3792 mL/kg	Difference between groups reported as non-significant; P value not reported

*For first 24 hours only. ETEC, enterotoxigenic *Escherichia coli*; L, litres; NA, not available.

TABLE **GRADE evaluation of interventions for diarrhoea in adults (acute)**

Important outcomes		Symptom control, duration of illness, hospital admission rates, cure rates, adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
What are the effects of treatments for acute diarrhoea in adults living in resource-rich countries?									
1 (152) [11]	Symptom control	Diphenoxylate *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (152 [11]	Duration of illness	Diphenoxylate *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
2 (670) [13] [14]	Duration of illness	Loperamide hydrochloride *v* placebo	4	0	0	0	0	High	
2 (670) [13] [14]	Duration of illness	Loperamide hydrochloride *v* loperamide oxide	4	0	0	0	0	High	
5 (1400) [12] [13] [14] [15] [16]	Duration of illness	Loperamide oxide *v* placebo	4	0	0	0	0	High	
1 (168)] [17]	Duration of illness	Racecadotril *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (71) [18]	Symptom control	Racecadotril *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
3 (288) [19] [20] [21]	Duration of illness	Racecadotril *v* loperamide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (157) [21]	Symptom control	Racecadotril *v* loperamide	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
5 (676) [22] [23] [24] [25] [26]	Duration of illness	Antibiotics *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
5 (676) [22] [23] [24] [25] [26]	Symptom control	Antibiotics *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for conflicting results
4 (574) [23] [24] [25] [26]	Cure rates	Antibiotics *v* placebo	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results. Consistency point deducted for different results at different endpoints
1 (71) [27]	Duration of illness	Restricted diets *v* unrestricted diets	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
What are the effects of treatments for mild-to-moderate diarrhoea in adults from resource-rich countries traveling to resource-poor countries?									
2 (277) [28] [29]	Duration of illness	Loperamide hydrochloride *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
2 (227) [28]	Duration of illness	Loperamide hydrochloride alone *v* trimethoprim-sulfamethoxazole	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (447) [33]	Cure rates	Empirical antibiotics *v* placebo (multiple destination studies)	4	0	0	0	0	High	
5 (1178) [31] [32] [28] [35] [36]	Duration of illness	Empirical antibiotics *v* placebo (multiple destination studies)	4	0	0	0	0	High	
9 (1315) [28] [34] [35] [36] [37] [39] [40] [42] [43]	Duration of illness	Empirical antibiotics *v* placebo (Central America)	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (195) [44]	Symptom control	Empirical antibiotics *v* placebo (North and West Africa)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results

Important outcomes		Symptom control, duration of illness, hospital admission rates, cure rates, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (47) [45]	Duration of illness	Empirical antibiotics *v* placebo (Asia)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (142) [46]	Duration of illness	Empirical antibiotics *v* each other (multiple destination studies)	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (94) [38]	Duration of illness	Empirical antibiotics *v* each other (Central America)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (102) [44]	Symptom control	Empirical antibiotics *v* each other (North and West Africa)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (79) [47]	Duration of illness	Empirical antibiotics *v* each other (Asia)	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
6 (unclear) [50]	Cure rates	Antibiotics plus antimotility agents *v* antibiotics alone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for heterogeneity among RCTs (regimens used, variable effects, and pathogens)
5 (unclear) [50]	Duration of illness	Antibiotics plus antimotility agents *v* antibiotics alone	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for heterogeneity among RCTs (regimens used, variable effects, and pathogens)
1 (227) [28]	Duration of illness	Antibiotics plus antimotility agents *v* antimotility agents alone	4	–1	0	0	0	Moderate	Quality point deducted for incomplete reporting of results
1 (142) [51]	Duration of illness	Different antibiotics plus antimotility agents regimens *v* each other	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and sparse data
1 (111) [52]	Symptom control	Bismuth subsalicylate *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (245) [53]	Duration of illness	Bismuth subsalicylate *v* placebo	4	0	0	0	0	High	
1 (203) [54]	Duration of illness	Bismuth subsalicylate *v* loperamide	4	0	0	0	0	High	
1 (219) [55]	Symptom control	Bismuth subsalicylate *v* loperamide	4	0	0	0	0	High	
2 (355) [56] [57]	Duration of illness	Zaldaride maleate *v* placebo	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for unclear generalisability
1 (179) [57]	Symptom control	Zaldaride maleate *v* loperamide	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (105) [58]	Duration of illness	Restricted diet *v* unrestricted diet	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for inclusion of intervention (different antibiotics)
What are the effects of treatments for mild-to-moderate diarrhoea in adults living in resource-poor countries?									
2 (185) [63] [60]	Symptom control	Antimotility agents *v* placebo	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (945) [62]	Duration of illness	Racecadotril *v* loperamide	4	0	0	0	0	High	
2 (446) [61]	Symptom control	Antibiotics *v* placebo	4	–2	0	0	0	Low	Quality points deducted for incomplete reporting of results and for no intention-to-treat analysis

Important outcomes		Symptom control, duration of illness, hospital admission rates, cure rates, adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (57) [64]	Symptom control	Citrate oral rehydration solution *v* bicarbonate oral rehydration solution	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (60) [65]	Symptom control	Commercial oral rehydration solution *v* standard oral rehydration solution	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for no direct statistical analysis between groups
What are the effects of treatments for severe diarrhoea in adults living in resource-poor countries?									
1 (88) [66]	Duration of illness	Antibiotics plus antimotility agents *v* antibiotics	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (110) [67]	Duration of illness	Racecadotril *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
1 (110) [67]	Symptom control	Racecadotril *v* placebo	4	–1	0	0	0	Moderate	Quality point deducted for sparse data
2 (565) [68] [69]	Duration of illness	Berberine *v* placebo or no treatment	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for assessing different outcomes
2 (565) [68] [69]	Duration of illness	Berberine plus tetracycline *v* tetracycline	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for measuring different outcomes
1 (165) [69]	Symptom control	Berberine *v* placebo or no treatment	4	–2	0	0	0	Low	Quality points deducted for sparse data and incomplete reporting of results
1 (46) [70]	Duration of illness	Chlorpromazine *v* placebo	4	–2	0	–1	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness point deducted for narrow inclusion criteria
1 (410) [71]	Symptom control	Chlorpromazine *v* placebo	4	–1	0	–3	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for assessing different outcomes and in a different population, and for additional interventions
2 (205) [72] [73]	Symptom control	Amino acid oral rehydration solution *v* standard oral rehydration solution	4	–2	0	–2	0	Very low	Quality points deducted for sparse data and incomplete reporting of results. Directness points deducted for assessing different outcomes and generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
4 (228) [74]	Duration of illness	Rice-based oral rehydration solution *v* glucose-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for weak methods (allocation concealment, blinding). Directness point deducted for unclear generalisability of results (RCTs in people positive for *Vibrio cholerae*)
4 (at least 409) [74]	Symptom control	Rice-based oral rehydration solution *v* glucose-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for weak methods (allocation concealment, blinding). Directness point deducted for unclear generalisability of results (RCTs in people positive for *V cholerae*)
1 (123) [75]	Symptom control	Rice-based oral rehydration solutions *v* low-glucose oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability of results (RCT in people positive for *V cholerae*)

Important outcomes		Symptom control, duration of illness, hospital admission rates, cure rates, adverse effects							
Number of studies (participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
1 (123) [75]	Duration of illness	Rice-based oral rehydration solutions *v* low-glucose oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability of results (RCT in people positive for *V cholerae*)
1 (123) [75]	Duration of illness	Low-sodium rice-based oral rehyration solution *v* rice-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability of results (RCT in people positive for *V cholerae*)
1 (123) [75]	Symptom control	Low-sodium rice-based oral rehyration solution *v* rice-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability of results (RCT in people positive for *V cholerae*)
1 (48) [74]	Duration of illness	Other polymer-based oral rehydration solution *v* glucose-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for unclear generalisability of results (RCT in people positive for *V cholerae*)
1 (50) [74]	Symptom control	Other polymer-based oral rehydration solution *v* glucose-based oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for subjective outcome
2 (310) [76] [77]	Duration of illness	Bicarbonate oral rehydration solution *v* standard oral rehydration solution	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for additional intervention in one groups and generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
2 (310) [76] [77]	Symptom control	Bicarbonate oral rehydration solution *v* standard oral rehydration solution	4	–1	0	–2	0	Very low	Quality point deducted for incomplete reporting of results. Directness points deducted for additional intervention in one groups and generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
1 (60) [78]	Duration of illness	Bicarbonate oral rehydration solution *v* chloride standard oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
1 (60) [78]	Symptom control	Bicarbonate oral rehydration solution *v* chloride standard oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
4 (575) [79] [80] [75] [81]	Duration of illness	Reduced osmolarity oral rehydration solution *v* standard oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
4 (575) [79] [80] [75] [81]	Symptom control	Reduced osmolarity oral rehydration solution *v* standard oral rehydration solution	4	–1	0	–1	0	Low	Quality point deducted for incomplete reporting of results. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)

Important outcomes		Symptom control, duration of illness, hospital admission rates, cure rates, adverse effects							
Number of studies (participants)	**Outcome**	**Comparison**	**Type of evidence**	**Quality**	**Consistency**	**Directness**	**Effect size**	**GRADE**	**Comment**
1 (20) [82]	Duration of illness	Intravenous rehydration *v* enteral rehydration	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)
1 (20) [82]	Symptom control	Intravenous rehydration *v* enteral rehydration	4	–1	0	–1	0	Low	Quality point deducted for sparse data. Directness point deducted for generalisability of results (comparing response in people with cholera with less severe forms of diarrhoea)

Type of evidence: 4 = RCT. Consistency: similarity of results across studies.
Directness: generaliseability of population or outcomes.
Effect size: based on relative risk or odds ratio.